PROCESS VALIDATION OF

GRISEOFULVIN TABLETS

Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University, Chennai

in partial fulfillment for the award of degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted By

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UNDER THE GUIDANCE OF

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EVALUATION CERTIFICATE

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INTERNAL EXAMINER **EXTERNAL EXAMINER**

Date: Date:

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LIST OF ABBREVATIONS

AQL	Acceptable Quality Limits
Vμ	Apparent volume obtained in ml.
BMR	Batch Manufacturing Record
BPR	Batch Packing Record
cGMP	Current Good Manufacturing Practice
^{o} C	Degree Centigrade
@	Does not contribute to the final mass of the product
FBD	Fluidised Bed Dryer
GC	Gas chromatography
GRIS	Griseofulvin
HPLC	High performance liquid chromatography
HCI	Hydrochloride
IH	In House Specifications
IP	Indian Pharmacopoeia
IR	Infrared spectroscopy
ICH	International Conference on Harmonization
KF	Karl Fisher Apparatus
***	LOD compensation
LOD	Loss on Drying
mg	Milligram
mm	Millimetre
M	Molar
nm	Nano meter
NLT	Not Less Than
NMT	Not More Than
PPM	Parts per Million
WHT	Pharmatest (Weight, Height, Thickness)
% w/w	Percentage weight/weight
PVC	Polyvinyl chloride
KI	Potassium Iodide
PVG	Process Validation Griseofulvin
$	Quantity of Griseofulvin has to be compensated
***	Quantity of Maize starch to get 100 % Assay
*	Quantity to be taken based on 100 % Assay
RMG	Rapid Mixer Granulator
RH	Relative Humidity
RSD	Relative Standard Deviation
RPM	Revolutions per Minute
NaOH	Sodium Hydroxide
#	Sieve size
SOP	Standard operating Procedure

V_f	Tapped final volume obtained in ml.
TLC	Thin layer chromatography
UV	Ultra Violet spectroscopy
US-FDA	United States Food and Drug Administration
USP-NF	United States Pharmacopoeia and National Formulary
W	Weight of the substance taken in grams

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1. INTRODUCTION

1.1.VALIDATION

Validation is the study of demonstrating and documenting at a manufacturing process operates efficiently.

The **pharmaceutical process validation** refers that it should cover all the critical parameters in a manufacturing process for a pharmaceutical dosage form, from designing a process to final validation of that the formulation in the large scale production.

Accordingly it is obvious that compliance with the finished product specification itself may not be sufficient to assure that the processes are valid and the manufacturer has full control over the process. [1]

However, Validation is an essential part of Quality Assurance Program and is fundamental to an efficient production operation. [2]

In the *Federal Register* FDA issued a notice on May 11, 1987 (52 FR 17638), the availability of guidelines entitling *Guidelines on General Principles of Process Validation* (the 1987 guidance). [3]

FDA has the authority of responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing process quotes that drug products be produced requires a high degree of assurance for meeting all the predetermined specifications they are intended to meet (21 CFR 211.100(a) and 211.110(a)). [3]

Effective process validation leads ultimately to an assured drug quality. The fundamental objective of quality assurance is that a product produced should be fit for its intended use.

This principle incorporates the understanding that the following conditions exist: [4]

1. Quality, safety, and efficacy are to be designed in the product.
2. In-process and finished-product inspection or testing is not sufficient to assure the quality of the product.
3. Every step of the process should be controlled for an assured finished product that meets all the quality attributes including predetermined specifications.

1.2.DEFINITIONS

EUROPEAN COMMISSION (E.C)

1991 - "Validation: Act of proving, in accordance of GMPs that any manufacturing Process actually leads to expected results". [1]

USFDA 1987

US Food and Drug Administration, 1987 "Process Validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre established limits and quality attributes." [3]

USFDA 2011

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is able to produce a product with high quality constantly. [4]

WORLD HEALTH ORGANISATION (W.H.O)

"Action of providing that any procedure, process, equipment, material, activity, or system actually leads to the expected results." [5],

1.3.REASON FOR PERFORMING PROCESS VALIDATION

The principle goal for validation is to assure, completely, that all the manufacturing processes, procedures and machinery being used should ensure safety, quality and strength of that formulation. Validation is very eminent, if there are any prominent changes to the premises, the facilities, the process or the equipment which may interferes with the quality of that product, directly or indirectly, partially or fully, should be validated. [6]

A process should also be validated to meet regulatory requirements. The Regulatory bodies, such as the FDA, shall need process validation. The US-FDA Quality System Regulation requires manufacturers to perform validation when the process is not completely verified by an appropriate inspection or test. [7]

A properly and completely validated, controlled process results in little scrap or re-processing, leads an increased output. Consistent compliance to specifications also results in fewer complaints and recalls. Whenever needed, the validation document contains the data to assist any improvements in a process or in the design of the next generation of the process. [8]

1.4.STAGES AND GENERAL PRINCIPLE TO PROCESS VALIDATION [5]

Process validation includes a series of activities taking place throughout the outcome of the product. They are:

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage are in accordance with the development and scale-up activities.

Stage 2 – Process Qualification: In this stage, the process design is evaluated to determine, whether the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Further assurance is attained during regular production that the process remains in a state of control.

1.4.1. Process Design: Stage 1

This is the step where building and capturing of the process knowledge and understanding took place. Process Design includes Research and development(R&D), formulation design, pilot plant scale-up techniques, TTG for commercial manufacturing of batches, determining stability parameters & storage conditions, handling of in-process quality assurance and finished forms of product, equipment, operational and installation qualification, master documents and process capacity.

1.4.2. Process Qualification: Stage 2

This stage is confirmation that the process design is capable of reproducing the manufacturing process. It confirms that all pre determined limits of the Critical Process Parameters are valid and that quality products can be produced even under "worst case" conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before marketing of a product.

1.4.3. Continued Process Verification: Stage 3

The Validation Maintenance Stage requires a frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures; changes if any in the manufacturing process, Standard operating procedures are employed, in addition to change control procedures.

Before commercial distribution of any batch, the manufacturer should have complete assurance of process performance. A proper understanding, knowledge and approach to production process may lead to a successful validation of a product.

1.5. CONCEPT OF VALIDATION [9]

The concept of validation is to ensure a steady production of a quality product throughout its life cycle that includes the critical aspects of ICH Q8, Q9 and Q10 guidelines. It makes sure that the process, equipment, materials and finished product produce a product having quality and purity as per the patient/customer requirements. Both FDA and cGMP states that control procedure shall be established to monitor output and to validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in process materials and drug materials.

1.6 SCOPE OF PROCESS VALIDATION

Process validation acts as a tool for the pharmaceutical manufacturing companies to ensure the manufacturing process including instruments and facilities are in a state of control and also to provide evidence that the final product meets the quality, purity and integrity as specified.

1.7. TYPES OF PROCESS VALIDATION [10]

The four types of process validation are:

1.7.1. Prospective Validation

In Prospective Validation, the validation protocol is implemented before the manufacturing process is put into commercial use. During the product development phase the manufacturing process should be divided into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to establish the critical parameters that may alter the quality of the finished product. A series of experiments should be designed to determine the cruciality of these factors. Each experiment should be planned and documented in an authorised protocol.

All equipment, production atmosphere and the analytical testing procedures and methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the manufacturing process have been identified and machine settings, component specifications and environmental conditions have been pre-determined.

It is generally taken acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality with a proper validation of the process. It is an assurance on the commercial three batches before marketing.

After completion of the review, the recommendations should be made on the extent of monitoring and the in-process controls needed for routine production. These should be included into the batch manufacturing and packaging record or into appropriate Sops. The deviations if any must be specified and appropriate steps to be taken in case of exceeding limits and frequencies.

1.7.2. Concurrent Validation

Concurrent validation may be the practical approach under certain circumstances. Examples such as when:

1. A previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site.
2. The product is a different strength of a previously validated product with the same ratio of active/inactive ingredients.
3. The number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control
4. The number of batches produced is limited (e.g. orphan drugs).
5. Process with low production volume per batch (e.g. radiopharmaceuticals, anticancer)
6. Process of manufacturing urgently needed drugs due to shortage (or absence) of supply.

The proper cause and reason to perform validation should be evidenced by document. And the Validation Team must approve the validation protocol. A summary report must be made and approved before marketing of any batch. After completing approval for all commercial batches a final report is established. It is usually said, acceptable that a minimum of three consecutive batches within the specification limits and with desired quality will lead to a complete validation study.

1.7.3. Retrospective Validation

In many establishments, the processes that are stable and in regular use have not undergone a formally documented validation process. Historical data may be used to provide necessary documentary evidence that the processes are validated. The steps involved in this type of validation need the preparation of a protocol, the reporting of the results of the data review, leading to a conclusion and Recommendation. Retrospective Validation stage possesses flow charts of process, BMR, In-process & finished product test results with trends and stability studies, premises, maintenance and equipment/instrument log books.

In retrospective validation studies, it is generally considered acceptable that data from a minimum of ten consecutive batches produced be utilized. When less than ten batches are available, it is considered that the data is not enough to demonstrate retrospectively that the process is fully under control. In such cases the study should be added with data generated with concurrent or prospective validation.

Some of the basic aspects of Retrospective Validation are

• Batches done for a determined duration (minimum of 10 last consecutive batches).
• Number of batches marketed per annum.
• Batch size, strength, manufacturer, time period.
• BMR/BPR (manufacturing & packing records).

1.7.4. PROCESS RE-VALIDATION

Re-validation is generally done to confirm the initial validation for a Periodic review. Re-validation provides the evidence that alterations in a process and /or the process environment that are introduced does not adversely affect process Characteristics and product quality. Documentation requirements shall be the same as for the initial validation of the process. Re-validation becomes essential in particular situations.

These are few examples of the modifications which may need re-validation:

1. Changes in raw materials (physical properties such as density, viscosity, particle size distribution, and moisture, etc., that interferes with the quality of a process or product).
2. Changes in the source of active raw material manufacturer.
3. Changes in packaging material (primary container/closure system).
4. Changes in the process (ex: drying temperatures, time of mixing etc)
5. Changes in the equipment (ex: addition of automatic detection system). The replacement of equipment may normally not require a re-validation unless the new equipment is approved for qualification.
6. Changes in the plant/facility.
7. Variations revealed by trend analysis (e.g. process drifts).

A decision not to perform re-validation studies must be fully justified and documented.

1.8. CHANGE CONTROL

Clearly defined procedure is needed to control any changes in the manufacturing processes. These procedures must control all the planned changes and ensure the presence of adequate supporting data which shows that modified manufacturing process will yield a product of desired quality.

Significant changes if any, to process (e.g. mixing time, drying temperature, etc.), using new equipments with different operating parameters, etc may require the pre-approval. If a change is proposed in any of the procedures, product, processes, or equipment, which may affect the quality, proper written procedures should be placed.

1.9. IMPORTANCE OF PROCESS VALIDATION [6]

1. Compliance to Regulatory bodies
2. Assurance in quality
3. Optimization in the process
4. Reduced cost of production
5. Reduction in Batch failures, enhancement in efficiency and productivity
6. Lowering down time
7. Reduced rejections
8. Increased output
9. Minimum complaints about process–related failures.

1.10. PROCESS VALIDATION PROTOCOL (IH)

TABLE: NO. 1

S.No	Process validation protocol
1	Objective
2	Lable claim
3	Validation team and responsibility
4	Scope of the protocol
5	Manufacturing formula
6	process flow chart
7	Rationale for selection of critical steps and its process parameters for validation
8	Critical steps, variables to be studied, measured response & acceptance criteria
9	Prerequisites for process validation
10	Yield details
11	General tests of raw material/packing material
14	List and qualification of equipments/instruments
15	Manufacturing and sampling procedures at different stages of process validation
	1. Sifting
	2. Dry mixing
	3. Sampling point diagram of rmg
	4. Granulation
	5. Drying
	6. Sampling point diagram of fbd
	7. Blending
	8. Sampling point diagram of blender
	9. Compression
	10. Coating
	11. Sampling point diagram of coating pan
	12. Dissolution profile
	13. Packing
	14. Stability studies

16	Process validation report
	1. Test results for raw materials
	2. Dry mixing
	3. Granulation
	4. Drying
	5. Blending
	6. Compression
	7. Coating
	8. Dissolution profile
	9. Blister packing
	10. Yield details
	11. Finished product report
	12. Stability report
17	Discussion
18	Future scope

1.11. REGULATORY REQUIREMENTS FOR THE PROCESS VALIDATION [5]

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable necessity under section 501(a) (2) (B) of the Act (21 U.S.C. 351(a)(2)(B)), gives about:

A drug shall be said to be adulterated if, the procedures used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current GMP to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it is intended to possess.

The cGMP regulations needs that manufacturing processes be framed and controlled to establish that in-process materials and the finished product meets the predetermined quality attributes, consistently and reliably.

1.12. HISTORY OF PROCESS VALIDATION [4, 11]

The emphasis on validation began in the late 1970s; the necessity has been around since at least the 1963 cGMP regulations for finished products.

The Kefauver-Harris Amendments to the FD&C Act were approved in 1962 with Section 501(a) (2)(B) as an amendment. Before that, cGMP, validation is not mandatory by law. The FDA had the hurdle of assuring that a drug was adulterated by collecting and analyzing samples.

This was a great regulatory burden and restricted the value of factory inspections of pharmaceutical manufacturers. The Kefauver–Harris amendments result was that the Federal Drug Administration need to declare a drug product is adulterated, if the manufacturing process was not validated.

Section 505(d)(3) is also significant in the implementation of process validation requirements as it gives the authority to withhold approval of a new drug application if the "methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are not sufficient to record that drug's strength, quality, identity and purity.

1.13. MASTER MANUFACTURING DOCUMENT

An eminent prospective validation program must be assisted by documentation extending from product initiation to full-scale production. A complete documentation can be referred to as the master documentation file. It provides a full product history that is being produced. The master documentation file must contain all information that was generated during the entire product development sequence to a validation process. [10]

The documents should be checked for data accuracy and adequacy as required by the FDA's guidelines.

Documentation covers the items, which should be compiled in a timely manner, are: [12]

1. Process challenging and characterization reports that contain a full description of the studies performed
2. Development batch record
3. Raw material test methods and specifications
4. Equipment list and qualification and calibration status
5. Process flow diagram
6. Process variable tolerances
7. Operating instructions for equipment (where necessary)
8. In-process quality control program, including:
    a. Sampling intervals
    b. Test methods
    c. Finished Product
    d. Stability
9. Critical unit operation
10. Final product specifications
11. Safety evaluation
12. Chemical
13. Process
14. Special production facility requirements
15. Cleaning
    a. Procedure for equipment and facilities
    b. Test methods
16. Stability profile of the product
17. Produced during process development
18. Primary packaging specification

A report is prepared which cross – refers the validation protocol, and that summarizes the obtained results, explores deviations (if any), draws conclusions that includes recommending changes to correct the deviations. Any change to the plan as mentioned in the protocol must get documented with appropriate justification. [13]

1.14. VALIDATION MASTER PLAN: [14]

A validation master plan is a document that concludes the company's overall history, intentions goals and approaches to be used for establishing performance adequacy. The Validation Master Plan should be accepted by management.

Validation in general requires a serious preparation and keen planning of the various stages in the manufacturing process. In addition, all work should be carried out in a planned way as per formally authorised Sops. All observations must be documented and where possible results must be recorded as actual numerical results.

The validation master plan should give an overview of the complete validation program, its organizational structure, its contents and plans. The principle components of it are the list/inventory of the items to be validated and the planning schedule.

All validation activities relating to critical technical operations, related to product and manufacturing process controls within an organisation must be incorporated in the validation master plan. It may refer to existing documents such as policy documents, SOP's and validation protocols and reports, but it must not repeat information documented anywhere.

The format should contain:

1. BMR
2. Master formula
3. Flow charts of the process
4. Master manufacturing and packaging guidelines
5. Specifications
6. Sampling (point of location and number)
7. Methods for performing tests
8. validation data of the process

1.15. STAGES AND PARAMETERS PERFORMED DURING PROCESS VALIDATION

TABLE: NO. 2

Stage	Process variables	Tests performed
Dry mixing	Mixing time	Uniformity of content, Bulk density, moisture content, sieve analysis
Granulation	Mixing time impeller reading during mixing	
Drying	Inlet & outlet temperature drying time	Final drying, Loss on drying/moisture content
Blending	Blending time	Uniformity of content & RSD
		Bulk density, sieve analysis & compressibility index
Compression	Pre compression studies	Optimum speed-Dissolution at lower & higher thickness
Compression	Machine speed (10 - 30 rpm)	At different speeds
		Appearance
		Group weight variation
		Individual weight variation
		Thickness
		Hardness
		Friability
		Disintegration time
		Dissolution
		Content uniformity
		Assay
Compression	Hopper study at maximum speed	Full hopper, middle of hopper & near end of hopper
		Individual weight variation
		Thickness
		Hardness
		Friability
		Disintegration time
		Content uniformity

Coating	Inlet temp. Exhaust temp. Pan speed atomization pressure, spray rate gun distance	Weight build up
		At the end of coating
		LOD
		Dissolution profile at 15, 20, 30, 45 & 60 minutes
Blister packing	Machine speed, forming and sealing temperature	Blister appearance and quality, leak test and impurity

1.17. BATCHES STUDIED FOR PROCESS VALIDATION

A. BATHCES FOR RAW MATERIALS

PVG01- Process Validation of Griseofulvin Tablets
PVG02- Process Validation of Griseofulvin Tablets
PVG03- Process Validation of Griseofulvin Tablets

B. BATHCES FOR FINISHED PRODUCT

GRIS01- Griseofulvin Tablets
GRIS02- Griseofulvin Tablets
GRIS03- Griseofulvin Tablets

2. AIM AND OBJECTIVE

- The present study is “Process Validation of Griseofulvin”.
- The company is involved in the manufacturing and distribution of a wide range of Pharmaceutical products.
- The present study “Process Validation of Griseofulvin 375 mg Tablets”, is designed in meeting the US-FDA requirements to scientifically prove that the finished product meet its predetermined specifications and Quality attributes.
- The major objective of the study is to systemically conduct the validation studies pertaining to the manufacturing activities of Griseofulvin 375 mg Tablets.
- A validation protocol is established and based on that each stage of manufacturing process is to be monitored. Three consecutive batches of Griseofulvin should be validated.
- Samples are to be collected from respective stages and appropriate tests are to be carried out depending on the validation protocol. Results of all the tests are to be recorded, compared and based on that documentary evidence should be established to confirm that the manufacturing process of Griseofulvin consistently meet its predetermined specifications and Quality attributes.

3. REVIEW OF LITERATURE

Singh , et al., 2012 validation is a comprehensive programme within the industry to achieve a quality product. The multidisciplinary validation team must confirm the process characteristics and specific validation test for a product to ensure that all the quality parameters were achieved. Scientific information obtained during preformulation forms the basis for comprehensive validation process.[15]

Chawla N.S. et al., 2012 gave an overview on the role of Process Validation in Tablet manufacturing process. They have notified that the validation as a documented act which demonstrates whether a procedure, process, activity etc., gives consistently the expected results or not. They highlighted that the Process Validation is a must for any manufacturing process, because testing a sample of a final product is not considered sufficient evidence to demonstrate that every product meets its specifications. The data obtained from the results of three consecutive batches of tablets are essential for concluding a Process Validation.[16]

Parnitha.K, et al., 2012 have discussed about tablet manufacturing process including Pre/Post approval issues as per USFDA guidelines. The objective of their study is to document each stage of manufacturing process giving importance to validation and evaluation of pharmaceutical dosage forms. It also includes guidelines about some equipments such as Blenders, Dryers, Tablets and Capsule equipments, Coating equipment etc.[17]

Pandit D., Mishra A., 2011 Pharmaceutical validation guarantees the reliability and reproducibility of the manufacturing process. The article examines the need for pharmaceutical validation, the various approaches, processing stage and control variables and sampling plan related to tablets dosage form to scientifically prove that the process produces a quality product.[18]

Sunil.K.D., et al., 2011 In this study they have stated the process control is a major requirement of cGMP regulation for finished pharmaceutical products. It acts as a key element in acquiring quality of a product. They also specified the importance of process

validation as an integral part of process control. Process control is essential part in the quality assurance of pharmaceutical product.[19]

Bodavula S.S.R. el al., 2011 have studied process validation of fluconazole. According to his study CGMP and U.S. FDA's guidelines demands written procedures for production and process controls to assure that the drug products have the identity, strength, quality and purity. He has performed the validation study on bulk and finished product of fluconazole. He has also performed the pharmacokinetic studies in his research.[20]

Sharad K. et al., 2011 have done process validation of Azifast 500mg tablets. They says that the validation is a fundamental concept of GMP's and quality assurance programme. They have performed the validation programme for Azifast tablets in various critical stages and concluded that the results are in the state of control based on the analytical report.[21]

Pravin P. et al., 2011 has done research on the prospective process validation of Gliclazide tablet 80mg sold dosage formulation. The critical process parameters were identified with the help of optimization batches. The critical parameters involved in sifting, dry mixing, granulation, dry mixing, lubrication and compression stages were identified and evaluated. The report of the study concludes that validation data provides high degree of assurance that manufacturing process product meeting its predetermined specifications and quality attributes.[22]

Vandana B.P. et al., 2011 have studied prospective process validation of cimetidine 400 mg tablet dosage form. She has studied the critical process parameters including raw material specifications, packing material specifications, various stages of granulation and compression, dissolution studies for finished products. The report of the study conducted on three batches have concluded that validation of process delivers a quality products that meets the specifications.[23]

Kanakadurga D.N., Mrudula B.S., et al., 2010 have performed process validation of galantamine hydrobromide tablets where they have performed the validation of critical

steps during manufacturing as per validation protocol. They have monitored the environmental conditions during every step of manufacturing for all the three batches.[24]

Rohokale BS., et al., 2010 has studied the process development of nimusulide 100mg tablet. They have concluded three batches of nimusulide 100mg to confirm that the production process was robust and rugged. They have concluded that process is feasible in the pilot scale production.[25]

Venkataraveendranath T. et al., 2010 have performed the process validation of Citalopram hydrobromide tablets. They have mentioned the importance of process validation in the pharmaceutical manufacturing. The purpose of the study is to determine the validation of process, Qualification of equipment and Inprocess study to conclude that the control over the critical parameters in the production of tablets leads to finished product with quality and purity what the product suppose to contain.[26]

Bharathi R., 2010 has been found that validation concept is important essential tools for Quality Management in Pharmaceutical Industry. It provides verification and validation of manufacturing process. Validation consists of a series of activities which includes documenting the process data and also confirming that a quality product can be manufactured by the designed the processes. Validation is an evidence to confirm that the process is in a state of control.[27]

Raghunandanan R., 2009 has provides an information on Validation Aspect of Solid Dosage Form. They have discussed the complete picture regarding validation of a solid dosage form in the given facilities and process. Validation is not only a regulatory requirement but also firm essential. Benefits of validation include reduction in cost, elimination of number of rejections and reprocessing of manufactured batches, improves the yield and consistent quality maintenance.[28]

Westerhuis et al.2006 developed simple assessment of homogeneity in pharmaceutical mixing processes. Establishment of uniform mixing of active pharmaceutical ingredient (API) with excipients is a crucial in-process quality control in the manufacturing of solid dosage forms.[29]

Sharareh S.B., et al.2005 they have discussed the validation of drying process which plays a vital role in formation of uniform size granules. Parameters like inlet and outlet temperatures, product temperature and LOD are the critical variables In the drying process, that could have a possible effect on the quality of a product.[30]

Aleem Het al., **2003** has discussed about the Drugs which are critical elements in health care. All the pharmaceutical products must be manufactured with maximum quality. Finished product testing alone is not sufficient to assure the product quality. Quality assurance department must ensure the maintenance of product quality. Pharmaceutical companies perform the process validation in ensuring that the process functions as what it is intended to do.[31]

O. Okhamafe et al.2002 gave an overview of pharmaceutical validation and process controls in drug development. Manufacturing facilities and processes involved in pharmaceutical production show its significant impact on the quality of the finished products. This process includes raw material specifications and equipment qualifications in addition to in-process controls. The intention of validation is to monitor the performance of the manufacturing process and conclude it to be validated.[32]

Brenda M, Wenzel and Brent H.H., 2002 have found that pharmaceutical organizations have a training need for validation skills that cover the areas of protocol execution, protocol development, validation project management, and documentation control. This type of training is useful in the enhancement of knowledge about validation to the personnel's involved in process validation programme.[33]

Reiner Kirrstetter., 2002 has been found that process validation of Active Pharmaceutical Ingredients is most challenging topic. Validation is the essential tool, of US-FDA in ensuring the quality of a product and process involved. It includes cleaning validation, analytical method validation, computer system validation and equipment qualification that could have effect on quality and purity of a product are to be validated. The objective of validation study starts from initial product development till completion of the product. [34]

Gamal A. 2000 Has discussed the necessary components required for a successful validation programme to obtain a quality product with predefined specifications. He discussed the manufacturing of API and using it in the manufacturing of the coated tablet dosage forms.[35]

Robert A.nash et al., 1996 The author takes the reader through the various stages, phases, and steps in the product and process development sequence of solid-dosage form design (tablet and capsule) using process validation principles and practices. The challenge for the pharmaceutical industry as it approaches the next millennium is to streamline and/or simplify validation requirements without sacrificing product quality and process flexibility.[36]

Scott B., et al., 1996 has discussed the process validation and its importance in solid dosage forms. Process validation is initiated by monitoring and evaluating the process performance in order to ensure that the process will consistently deliver a quality product throughout its life cycle.[37]

Maynard D.W 1993 gave the importance of validation master plan in conducting the validation programme. The tests to be performed, sampling, Inprocess testing and qualification of the equipment plays a major role in the validation study. Documenting the results at each stage plays is mandatory as pre USFDA and GMP guidelines.[38]

Sharpe J.R. et al., 1986 A discussion on process validation as an important element in GMP of pharmaceuticals products is presented. The importance of validation is exemplified in the production of sterile and non-sterile products.[39]

4. MATERIALS AND METHODS

Objective

To establish scientific evidence that the manufacturing process will consistently produce **Griseofulvin tablets,** meeting its predetermined acceptance criteria and consistently deliver quality product.

Lable claim

Each film coated tablet contains:

Griseofulvin IP 375 mg

Responsibilities

TABLE: NO. 3

1	**Technology Transfer**	To prepare, review & approve the process validation protocol report.
2	**Production**	Execution of manufacturing process during validation. Review and approval of process validation protocol and report.
3	**Quality Control**	To analyze validation samples and review of Analytical report.
4	**Regulatory Affairs**	To review the protocol and report from Regulatory perspective.
5	**Quality Assurance**	To monitor the validation activity & sampling as per the sampling plan of protocol. Review and approval of process validation protocol and report.

Scope of protocol:

- The scope of this protocol is applicable to the validation of manufacturing process of Griseofulvin tablets to be carried out.
- If any batch (es) fails due to process extrinsic causes or deviations from the batch manufacturing record/protocol the batch (es) will be disqualified for validation purpose and fresh three consecutive batches shall be considered for validation.

4.1. MANUFACTURING FORMULA

TABLE: NO. 4

Granulation and Blending Materials			
S.No	**Materials**	**Grade**	**Category**
1	Griseofulvin *$	IP	Antifungal
2	Maize Starch **	IP	Diluent
3	Sodium Lauryl sulphate	IP	Disintegrant
4	Polyethylene glycol 6000	IP	Binding agent
5	Povidone (PVP K30)	IP	Binding agent
6	Purified water @	IP	Vehicle
7	Sodium Starch glycollate	IP	Disintegrant
8	Talc	IP	Glidant
9	Magnesium stearate	IP	Lubricant
10	Colloidal silicon dioxide	IP	Glidant
11	Maize Starch	IP	Disintegrant
12	Maize Starch *** (LOD compensation)	IP	LOD Compensation

TABLE: NO. 5

Coating Materials			
S.No	**COATING MATERIAL**	**Grade**	**CATEGORY**
1	Hypromellose 5cps	USP	Coating agent
2	Dichloromethane @	BP	Solvent
3	Isopropyl alcohol @	IP	Solvent
4	Glycerine	IP	Plasticizer

* Quantity to be taken based on 100 % Assay and 0 % Loss on drying.

$ Quantity of Griseofulvin has to be compensated with additional quantity, if process loss occurs during **Micronisation** in Fluid energy mill.

*** Actual quantity of Maize starch to be taken per lot = 12.360 Kg – additional quantity of drug taken to get 100 % Assay and 0 % Moisture content.

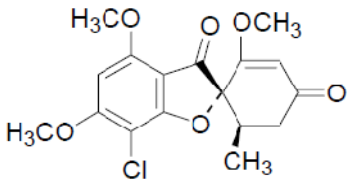
*** LOD compensation

@ Does not contribute to the final mass of the product.

4.2 DRUG PROFILE

4.2.1. GRISEOFULVIN [40, 41]

Structure:



Chemical name: Griseofulvin is (1*S*,6'*R*)-7-chloro-2',4,6-trimethoxy-6'-methylbenzofuran-2-spiro-1- cyclohex-2'-ene-3,4'-dione

Formula **:** $C_{17}H_{17}ClO_6$

Molecular weight **:** 352.8

Description:

A white to yellowish white powder, the particles of which are generally upto 5 µm in maximum dimension, although larger particles, which may occasionally exceed 30 µm may be present; almost odourless.

Melting point **:** 217°C-224 °C

Solubility

Freely soluble in *dimethylformamide* and in *1, 1, 2, 2-tetrachloroethane;* soluble in *acetone* and in *chloroform;* slightly soluble in *ethanol (95 per cent)* and in methanol; practically insoluble in *water. (Refer- Indian Pharmacopeia, volume I, pg 151, 2.4.26.Solubility of Griseofulvin)*

Category **:** Antifungal

Griseofulvin is fungistatic *in vitro* for various species of the dermatophytes *Microsporum, Epidermophyton,* and *Trichophyton.* The drug has no effect on bacteria or on other fungi.

Mechanism of Action [42]

A prominent morphological manifestation of the action of Griseofulvin is the production of multinucleate cells as the drug inhibits fungal mitosis. In mammalian cells treated with high concentrations, Griseofulvin causes disruption of the mitotic spindle by interacting with polymerized microtubules. The binding sites of Griseofulvin on the microtubular protein are distinct. In addition to its binding to tubulin, Griseofulvin also may bind to a microtubule-associated protein.

4.2.2. PHARMACOKINETIC DATA [43]

Absorption

The absorption of Griseofulvin from the gastrointestinal tract is variable and incomplete. On average less than 50% of the oral dose is absorbed, but administration after a fatty meal and a reduction in particle size will increase the rate and extent of absorption. Following oral administration there is a phase of rapid absorption, and there after a phase of slower prolonged absorption. Griseofulvin exhibits linear pharmacokinetics.

Distribution

The volume of distribution is about 0.7 L/Kg and the Griseofulvin is ca 80% bound to plasma proteins predominantly serum albumin. Griseofulvin crosses placental barrier and may be excreted in breast milk. There is selective deposition of Griseofulvin in newly formed keratin in hair, skin and nails, which gradually moves to the surfaces of these appendages.

Metabolism

Griseofulvin undergoes metabolism to inactive metabolites, principally 6-desmethylgriseofulvin or its glucoronide conjugate.

Excretion

The terminal half life ranges from 9.5 – 21 hours, with considerable intersubject variability. The majority of dose, principally as 6-desmethylgriseofulvin or as glucoronide conjugate are excreted in urine. With less than 1% administered dose being excreted as unchanged Griseofulvin. The reminder of the dose principally as metabolites, excreted in bile and faeces.

Therapeutic uses

Mycotic disease of the skin, hair, and nails due to *Microsporum, Trichophyton,* or *Epidermophyton* responds to Griseofulvin therapy. Infections that are readily treatable with this agent include infections of the hair (tinea capitis) caused by *Microsporum canis, Microsporum audouinii, Trichophyton schoenleinii,* and *Trichophyton verrucosum;* "ringworm" of the glabrous skin; tinea cruris and tinea corporis caused by *M. canis, Trichophyton rubrum, T. verrucosum,* and *Epidermophyton floccosum;* and tinea of the hands (*T. rubrum* and *T. mentagrophytes*) and beard (*Trichophyton* species). Griseofulvin also is highly effective in "athlete's foot" or epidermophytosis involving the skin and nails, the vesicular form of which is most commonly due to *T. mentagrophytes* and the hyperkeratotic type to *T. rubrum.* Since very high doses of Griseofulvin are carcinogenic and teratogenic in laboratory animals, the drug should not be used systemically to **treat trivial infections** that respond to topical therapy.

Untoward effects

The incidence of serious reactions associated with the use of griseofulvin is very low. One of the minor effects is headache. Other nervous system manifestations include peripheral neuritis, lethargy, mental confusion, impairment of performance of routine tasks, fatigue, syncope, vertigo, blurred vision, transient macular edema, and augmentation of the effects of alcohol. Among the side effects involving the alimentary tract are nausea, vomiting, diarrhea, heartburn, flatulence, dry mouth, and angular stomatitis. Hepatotoxicity also has been observed. Hematologic effects include leukopenia, neutropenia, punctate basophilia, and monocytosis are observed.

Contra indications

Hepatic disease and porphyria.

Storage

To be stored in a tightly closed container.

4.3. RATIONALE FOR SELECTION OF CRITICAL STEPS AND ITS PROCESS PARAMETERS FOR VALIDATION

4.3.1. DRY MIXING

The dry-mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). Sieve Analysis, Water Content, Tapped Density for the Dry mix pool sample has to be done. The content uniformity of active ingredient **Griseofulvin** has to be established after 5 minutes during dry mixing process. The mixing of the active ingredient depends on the mixing time and speed of RMG, which affect the uniform distribution of drug during mixing. These critical steps are to be validated during the Dry mixing process.

4.3.2. GRANULATION

The granulation step involves converting the powder into free flowing near spherical granular mass. The amount of granulation solution added, mixing speed and time are critical variables. These variables affect the

a) Granule strength(fines)
b) Bulk density of blend
c) Flow characteristics of granules

These in turn affects the quality attributes of tablets like weight variation, Hardness, Disintegration Time and Dissolution.

4.3.3. DRYING

The drying step involves drying of wet mass. Moisture content in granules is important factor. If moisture content is more in granules it will lead to poor flow and poor hardness. If moisture content is less it will lead to capping, high friability and chipping. During drying the desire LOD will be maintained in the granules which will influence the quality parameters like tablet hardness, flow properties of granules, physical properties during compression. Drying of granules in fluid bed equipment (FBE) controls the moisture content. Inlet temperature of FBD is most critical variable for the same. Moisture content is checked periodically to establish the same. During the drying process the following variables are to be studied.

1. Inlet temperature (^{o} C)
2. Outlet temperature (^{o} C)
3. Product temperature (^{o} C)
4. Loss on Drying (% w/w)

4.3.4. BLENDING

This step involves mixing of granules with other blending material. The purpose of blending is to get a uniform distribution of Griseofulvin IP. This is followed by mixing of the blend with Magnesium stearate and Talc (Lubrication) to get good flow and anti-adhesion property of the blend. Mixing speed and time are critical variables in this process. Mixing time is critical as under blending will result in non uniform distribution of drug and poor flow, whereas over blending will result in de-mixing leading to non uniform distribution of drug and increases in disintegration time. Proper blending is established by checking **Content uniformity & RSD (relative standard deviation)** of drug at all the time intervals (After 20, 25 & 30 min as per protocol) In addition to this, the following tests are to be done. They shall be carried out on final time interval samples only.

a) Moisture content
b) Sieve analysis
c) Bulk density
d) True density
e) Compressibility index
f) Assay

4.3.5. COMPRESSION

This step involves conversion of blended material into tablets as per specifications. The following are the variables considered for study during compression process.

1. Thickness
2. Speed of machine (10 - 20 RPM)
3. Hopper fill (Full, Middle & Near end)

Following parameters were considered to establish the above-mentioned variables at regular intervals

a) Dissolution values at different Thickness
b) Appearance
c) Group weight
d) Individual weight variation
e) Hardness
f) Friability
g) Disintegration
h) Thickness
i) Dissolution at different speeds (Griseofulvin IP)
j) Uniformity of content at different speeds (Griseofulvin IP)
k) Assay at different speeds (Griseofulvin IP)

4.3.6. COATING

The coating step involves the covering of tablet surface with a polymer film. In coating process pan RPM, temperature, spray rate, gun to bed distance and air pressure are critical process variables. These parameters affect the coating and final appearance of the tablets. Coating process is performed as per the instructions given in BMR. During the coating process, the initial weight of core tablets and final weight of coated tablets after coating are noted. Parameters to be considered for uniform coating of tablets are:

a) **Pan RPM**: If the RPM of coating pan is not within the specified limit then uneven distribution of the coating solution on tablet takes place.
b) **Inlet/Exhaust temperature**: If the temperature of coating pan is not within the specified limit then the drying will be insufficient which results twining and sticking of tablets or rough surface and cracking of the film.
c) **Spray rate**: If the spray rate is not proper then the coating will not be uniform.
d) **Gun to be distance:** If gun to be distance is not adequate, it results in rough surface or over wetting during coating.
e) **Air pressure**: If the compressed air pressure (Main and atomization) is not adequate, it results in peeling or rough surface of tablets.

4.3.7. BLISTER PACKING

This process involves packing of tablets in polythene lined aluminum foil and PVC blister pack. Temperature of rollers (sealing and forming) & speed of machine are critical variables. Adequate sealing roller temperature is essential to get proper sealing. Adequate forming roller temperature is essential to get proper blister formation. Less temperature will lead to leakage and higher of machine affects the following parameters.

a) Proper sealing of blister pack
b) Proper forming of blister pockets
c) Configuration of blister pack

Leak test and physical evaluation are the tests to be done to establish the above variables during blister packing operation.

4.3.8. STABILITY STUDIES

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a re-test period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period. Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

4.3.9. AREA MONITORING

The air present in the process areas is tested by the Setting Plate Technique and the microbial content present in the air was found to be within the specified limits.

4.4. FLOW CHART FOR PROCESS VALIDATION

4.4.1. GRANULATION STAGE

EQUIPMENT **PROCESS** **PROCESS VARIABLES** **TESTS PERFORMED**

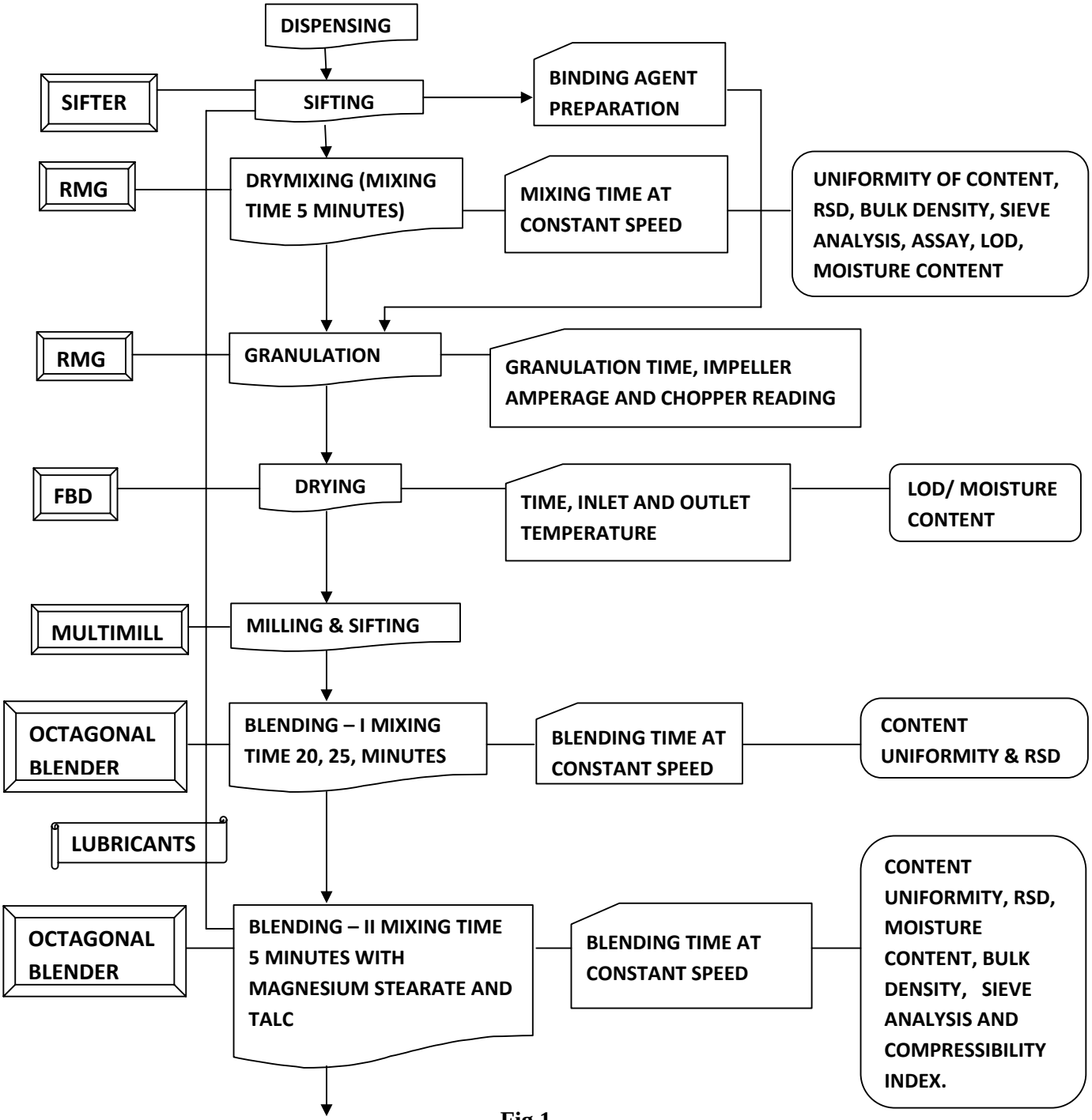


Fig.1

4.4.2. COMPRESSION STAGE

EQUIPMENT	PROCESS	PROCESS VARIABLES	TESTS PERFORMED
COMPRESSION MACHINE	COMPRESSION SPEED AT 10-20 RPM	MACHINE SPEED	GROUP WEIGHT VARIATION, INDIVIDUAL WEIGHT VARIATION, HARDNESS, THICKNESS, ASSAY, FRIABILITY,DISINTEGRATION TIME,CONTENT UNIFORMITY.

Fig.2

4.4.3. FILM COATING STAGE

EQUIPMENT	PROCESS	PROCESS VARIABLES	TESTS PERFORMED
AUTOCOATER	FILM COATING	INLET & OUTLET TEMPERATURE, SPRAY RATE, PAN RPM,ATOMIZATION PRESSURE	WEIGHT BUILD UP, DISSOLUTION PROFILE & ALL TESTS AS PER THE SPECIFICATIONS
	COATING SUSPENSION PREPARATION		
INSPECTION BELT	INSPECTION		
BLISTER PACKING	PACKING	SPEED,SEALING & FORMING TEMPERATURE	BLISTER QUALITY LEAK TEST & ALL TEST AS PER THE SPECIFICATIONS

Fig.3

4.5 CRITICAL STEPS, VARIABLES TO BE STUDIED, MEASURED RESPONSE & ACCEPTANCE CRITERIA

TABLE: NO. 6

Stage	Process variables	Time	Tests performed	Acceptance criteria
Dry mixing	Mixing time	5 minutes	Uniformity of content	100±15 % RSD NMT 6.0 %
			Bulk density, moisture content, sieve analysis	For information

TABLE: NO. 7

Stage	Process variables	Time	Tests performed	Acceptance criteria
Granulation	Mixing time impeller reading during mixing	As per BMR		

TABLE: NO. 8

Stage	Process variables	Time	Tests performed	Acceptance criteria
Drying	Inlet & outlet temperature drying time	Final drying	Loss on drying/moisture content	< 1.0 % w/w

TABLE: NO. 9

Stage	Process variables	Time	Tests performed	Acceptance criteria
Blending	Blending time	20 &25 minutes (20+5 min)	Uniformity of content & RSD	100±15 % RSD NMT 6.0 %
		30 minutes(25+5)	Uniformity of content & RSD	
			Assay, Moisture content, Compressibility Bulk density, sieve analysis & compressibility index	As per the current In process specification

TABLE: NO. 10

Stage	Process variables	Time	Tests performed	Acceptance criteria
Compression	Pre compression studies	Optimum speed	Dissolution at lower & higher thickness	As per current finished product specification
	Machine speed (10 - 20 rpm)	At different speeds	Appearance	White capsule shaped, uncoated tablets, plain on both sides
			Group weight variation	12.800g ± 2.0 % (12.540 g ± 13.060 g)
			Individual weight variation	640 mg ± 4%(614.00 mg – 666.00 mg)
			Thickness	4.70 mm ± 0.2 mm (4.50 mm – 4.90 mm)
			Hardness	NLT 3.0 kg/cm2
			Friability	NMT 1.0 % w/w
			Disintegration time	NMT 20 minutes
			Dissolution	NLT 80 % of Griseofulvin in 45 minutes
			Content uniformity	85 – 115 % of label claim
	Hopper study at maximum speed	Full hopper, middle of hopper & near end of hopper at optimum speed	Individual weight variation	640 mg ± 4% 9(614.0 – 666.0 mg)
			Thickness	4.70 ± 0.2 mm (4.50 – 4.90 mm)
			Hardness	NLT 3.0 kg/cm2
			Friability	NMT 1.0 % w/w
			Disintegration time	NMT 15 minutes
			Content uniformity	100 – 15 % of label claim

TABLE: NO. 11

Stage	Process variables	Time	Tests performed	Acceptance criteria
Coating	Inlet temp. Exhaust temp. Pan speed atomization pressure spray rate gun distance	Weight build up		As per current finished product specification
		At the end of coating	LOD	
			Dissolution profile at 5,15, 20, 30&45minutes	For information

TABLE: NO. 12

Stage	Process variables	Time	Tests performed	Acceptance criteria
Blister packing	Machine speed, forming and sealing temperature	Blister appearance and quality, leak test and impurity		As per sop

YIELD DETAILS

Record the yield at every stage as mentioned below.

Blending, Compression, Coating, Inspection and Packing

4.6. LIST OF EQUIPMENTS USED IN VALIDATION STUDY OF GRISEOFULVIN TABLETS

TABLE: NO. 13

S.No	Equipment used in Quality Control	Intended Use
1	HPLC(Aligant technology)	Impurities and Related substances
2	UV	Identification of compounds
3	IR	Identification of functional groups
4	GC	Qualitative & Quantitative Analysis
5	Muffle furnace	Purity of the compound (Ash Value)
6	Dissolution Apparatus	Drug release from the dosage form
7	Disintegration Time	To determine the time of Disintegration of tablets
8	WHT	Weight, Hardness, Thickness Tester
9	Melting Point Apparatus	Calculate the melting point of the given raw material
10	Bulk and true Density apparatus	To ensure the particle size/granules size
11	Sieve shaker	To calculate the percentage retains of raw materials
12	Karl fisher apparatus	Calculate the moisture content
13	Sonicator	To remove the dissolved gases/Uniform mixing
14	Hot air oven	Drying
15	Ultra filtration (0.45µm)	Preparation of HPLC mobile phase
16	Electronic/Analytical balance	To weigh accurate quantity of substances
17	Ph	To check the pH of the given solution

TABLE: NO. 14

S.No	Equipment used in Granulation	Intended Use
1	Sifter	To attain uniform sized powder particles/granules
2	Rapid Mixing Granulator	For Dry mixing and granulation
3	Fluid Bed Granulator	To achieve desired LOD of granules
4	Binder agent preparation vessel	Preparation of binding agent
5	LOD analyser	To check the LOD of the granules
6	Multi mill	Size reduction of Lumps
8	Octagonal blender	Blending of granules
9	Weighing Balance	Weighing the granules after blending

TABLE: NO. 15

S.No	Equipment used in Compression	Intended Use
1	Compression machine	To compress the granules in to tablets
2	Analytical balance	To check the group weight of tablets
3	Friabilator	To assess the effect of friction & shock (Tablet Strength)
4	WHT	To check the Weight, Hardness & Thickness of each tablet
5	Vernier	To check the thickness of each tablet

TABLE: NO. 16

S.No	Equipment used in IPQA	Intended Use
1	Analytical balance	To check the group weight and individual weight variation of tablets
2	Friabilator	To assess the effect of friction & shock (Tablet Strength)
3	WHT	To check the Weight, Hardness & Thickness of each tablet
4	Disintegration Time	To determine the time of Disintegration of tablets

TABLE: NO. 17

S.No	Equipment used in Coating	Intended Use
1	Neocota	Used for coating the uncoated tablets
2	CSP tank & Stirrer	Polymer solution preparation
3	Colloidal mill	Pigment solution preparation
4	Agitator	Mixing of both Polymer and Pigment solution

TABLE: NO. 18

S.No	Equipment used in Packing	Intended Use
1	Blister Packing machine	Primary Packing of the tablets
2	Leak test	To check the efficiency of the primary packing

All the Equipments used in the manufacturing of Griseofulvin tablets have been tested for

1. Installation qualification
2. Operational qualification and
3. Performance qualification

4.7. GENERAL TESTS FOR RAW MATERIALS

1. DESCRIPTION:

Colour, odour and physical state of the sample is identified by physical observation.

2. SOLUBILITY:

Soluble/Insoluble in specific solvents can be determined by the solubility test.

3. IDENTIFICATION:

The purity of raw material can be determined by Identification test. Various samples are identified by the various instruments like U.V., I.R., T.L.C., H.P.L.C., G.C., etc. In U.V and I.R sample absorbance is compared with standard absorbance. In T.L.C., sample R_f values are compared with the standard R_f value.

4. PH TEST:

Acidic/Basic/Neutral character of the substance can be determined by pH meter.

5. SPECIFIC OPTICAL ROTATION:

Optical rotation of the sample can be known by polari meter

6. IMPURITIES AND RELATED SUBSTANCES PRESENT:

Maximum, total amount of impurities and related substances present in the sample can be determined using HPLC method.

7. HEAVY METAL TEST (in PPM):

Heavy metals like As, Sb, Bi, Hg, Pb etc are present in the sample can be determined by this test.

8. SULPHATED ASH TEST (in PPM):

Amount of inorganic compounds present in the sample can be determined by this test.

9. MOISTURE TEST:

If drug contains highly moisture, it's function may be destroyed. Manufacturing process depends upon the moisture of raw materials.

Procedure:

Take the suitable quantity of anhydrous methanol in titration vessel and pour the accurate quantity of sample in it and titrate with K.F. reagent.

% of water = V × F × 100/Wt

Here V = Volume of Karl Fisher Reagent consumed for the sample titration.

F = Factor of Karl Fisher Reagent.

Wt = Weight of the sample in mg.

10. BULK DENSITY/TRUE DENSITY TEST:

The strength of the finished product depends upon the bulk density.

Procedure:

Mechanically tap the cylinder 500 times initially and measure the tapped volume (Vμ). Repeat the tapping an additional 750 times and measure the tapped volume (V_f).

Calculation:

Untapped density (Bulk Density) $= \frac{W}{V\mu}$ grams/c.c

Tapped density (True Density) $= \frac{W}{V_f}$ grams/c.c

W = Weight of the substance taken in grams

Vμ = Apparent volume obtained in ml.

V_f = Tapped final volume obtained in ml.

11. ASSAY:

Quantity of drug present in the sample can be determined by this test. Different methods like UV, IR, HPLC etc. are used to determine the assay.

12. FINENESS:

The granulation process depends upon the fineness of the raw materials.

Procedure:

Weigh the sample and transfer in to sieve and after sieving the retains are collected and weighed.

13. SIEVE ANALYSIS:

All the sieves arranged in such a way that sieves with smaller number (#16) should be present on the top and larger number (#200) at the bottom. Weigh about 10-15 gm of the material to be analyzed and transfer it over the vertically arranged sieves. Then they are places over sieve analyzer for a specified period of time. Later they are analyzed for the percentage of material retained on each sieve by collecting the materials separately and weighing.

4.8.GENERAL TESTS TO BE PERFORMED FOR PACKING MATERIAL

4.8.1. Aluminium foil

TABLE: NO. 19

S.No	Tests Performed
1	Appearance
2	Width
3	Thickness of aluminium foil
4	Aluminium foil Grammage
5	HSL(heat seal lacquer) coating Grammage
6	Printing
7	Pin holes/m2
8	Cello tape test
9	Shade
10	Other details(role shall be free from dust, foreign matter, rough edge, scratches, core damages)
11	AQL for defects

4.8.2. PVC clear film

TABLE: NO. 20

S.No	Tests Performed
1	Appearance
2	Colour
3	Width
4	Thickness of PVC clear film
5	Grammage
6	Other details(role shall be free from dust, foreign matter, rough edge, scratches, core damages)
7	AQL for defects

4.8.3. Carton

TABLE: NO. 21

S.No	Tests Performed
1	Appearance
2	Internal Dimensions: length
3	Internal dimensions: width
4	Internal dimensions: height
5	Grammage
6	Shade
7	AQL for defects

4.8.4. Sticker Hologram

TABLE: NO. 22

S.No	Tests Performed
1	Appearance
2	Dimensions - Length and width
3	Grammage of film and adhesive
4	Performance(should not tear without leaving hologram metallization on application to substrate after 30 min curing time)
5	General details(tackiness, appearance without wrinkles, easy to peel off from the release paper, uniform adhesive coating)
6	AQL for defects

4.8.5. Shipper

TABLE: NO. 23

S.No	Tests Performed
1	Appearance
2	Grammage of each ply
3	Thickness
4	Internal Dimensions: length
5	Internal Dimensions: Width
6	Internal Dimensions: Height
7	LOD

4.9.METHODOLOGY

MANUFACTURING AND SAMPLING PROCEDURES AT DIFFERENT STAGES OF PROCESS VALIDATION

4.9.1. SAMPLING PROCEDURE AT DIFFERENT STAGES

Three sets of samples were collected for content uniformity. One set of samples was used for analysis and the remaining two sets were kept as reserve sample.

4.9.2. DRY MIXING

The dry-mixing step was done for mixing of active ingredient with other additives in Rapid Mixer Granulator (RMG).The Content uniformity of Griseofulvin (API) was established at the end of 5 minutes during the validation of dry mixing process. The samples were withdrawn from 10 locations of the RMG as directed in the protocol (refer Fig)

The acceptance criterion for the content uniformity of Griseofulvin is 100 ± 10% of the theoretical quantity, whereas the limit for relative standard deviation (RSD) should be NMT 6.0%. The sample quantity is shall be between 448.857 gm to 1346.571 mg. Sampling was done with sampling rod. Samples were collected in tarred vials.

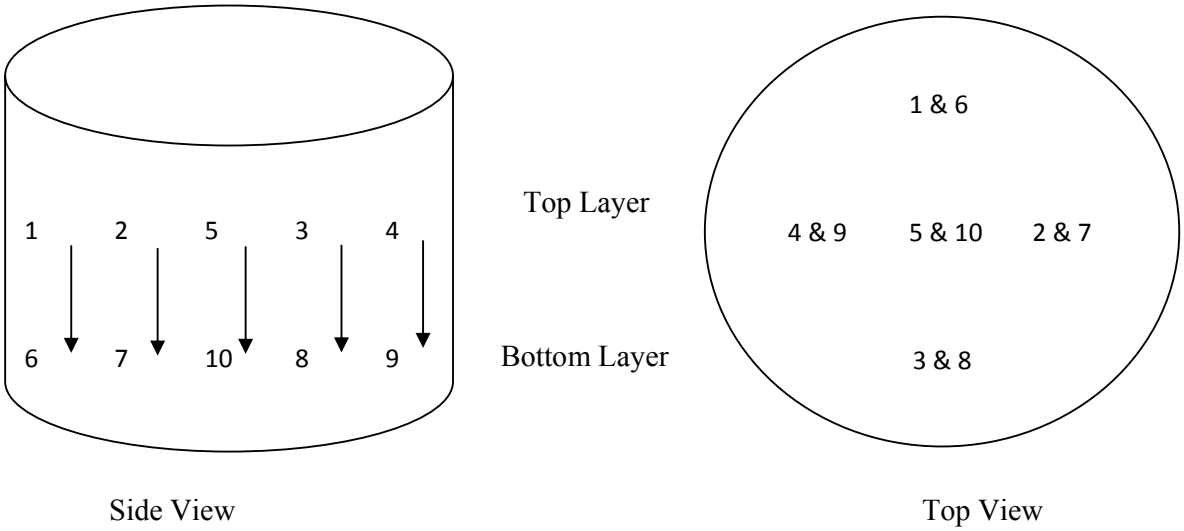


Fig.4 Rapid Mixer Granulator Sampling Locations

4.9.3. GRANULATION

The granulation was performed using RMG. The granulation step involves converting the powder in to wet dough mass. The granulation strength, bulk density of blend, dissolution, hardness of tablets etc are influenced by mixing time. Aqueous binding solution is used for granulation. The granulation end point is a critical process and the end point of granulation is determined by physical observation and Amperage reading of Impeller to correlate the granulation end point.

4.9.4. DRYING:

Moisture in granules or blend is important factor. If moisture content is more in granules it will lead to poor flow and Hardness. If moisture is less it will lead to capping, High friability and chipping. Drying of granules if, FBD controls the moisture content. Inlet temperature of FBD is most critical variable for the same. Moisture content is checked periodically to establish the same. The process of drying was carried out as per the batch manufacturing record at an inlet temperature of **40 ^{o}C – 50 ^{o}C** till the moisture content comes to less than **1% w/w**. Then the outlet temperature to correlate the moisture content. Samples were withdrawn from five different places of the FBD bowl after drying and moisture content was checked.

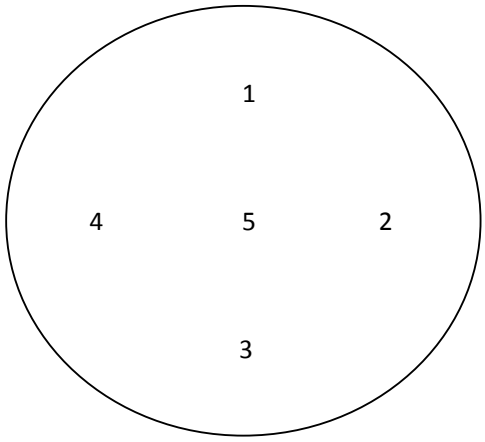


Fig.5. Sampling Locations for FBD after Drying of Granules

4.9.5. BLENDING:

Sifted materials and sized granules were loaded into the Octagonal blender except Magnesium stearate and talc. Blender was started in inch mode to check for any leakage of material. On ensuring that there is no leakage, the material was blended for 20 & 25 minutes and samples were collected from 10 locations as shown in the figure below. Magnesium stearate and talc were mixed with equal quantity of blend taken from blender after 25 minutes of initial blending time. They are added to the remaining blend material in blender and blending process is performed for 5 minutes and 10 samples were collected using sampling rod at the sampling locations mentioned in the diagram. Samples were collected in tarred vials and analyzed for the following tests:

1. Content uniformity & RSD
2. Sieve analysis
3. Bulk density
4. True density
5. Compressibility index
6. Assay
7. Moisture Content

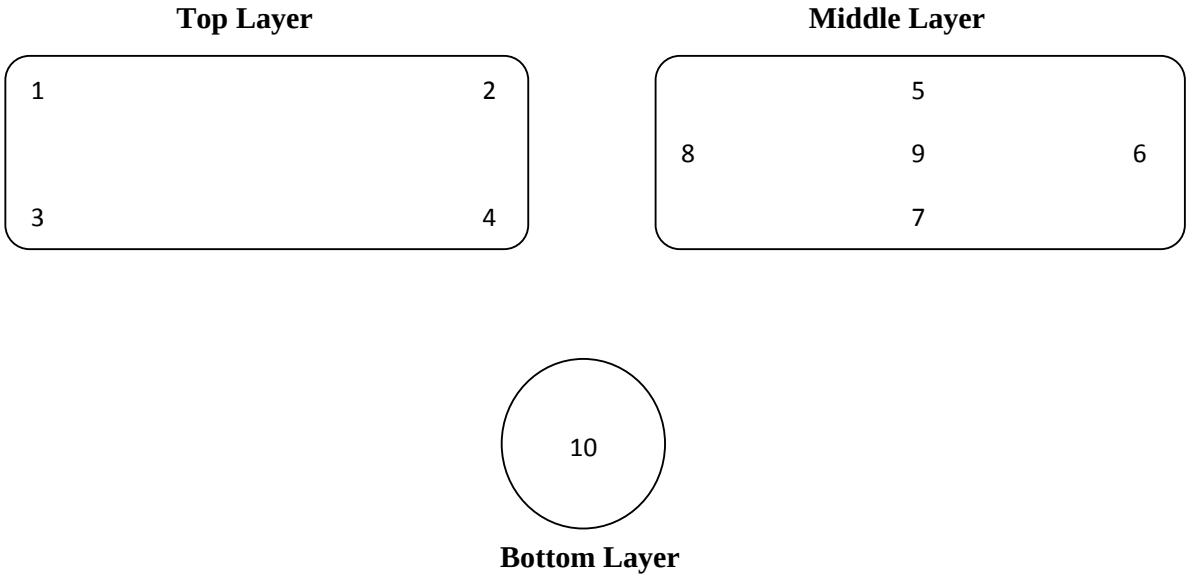


Fig.6. Sampling Locations for Blender after Blending

4.9.6. COMPRESSION

Compression was carried as per the Batch manufacturing record (BMR) with 8.5 mm × 16.5 mm shallow concave capsule shaped punches and dies and by setting the machine at different speed of 10-20 RPM and following parameters were checked.

Number of stations: **37**

Type of tooling: '**D**' type

PHYSICAL PARAMETERS TO BE CHECKED DURING COMPRESSION

TABLE: NO. 24

S.No	Parameters	Standard	No. of Tablets taken for testing
1	Appearance	White capsule shaped, uncoated tablets, plain on both sides	20 tablets
2	Weight of 20 tablets (group weight)	12.800 ± 2% (12.540 - 13.060 g)	20 tablets
3	Hardness	NLT 3.0 kg/cm²	6 tablets
4	Thickness	4.70 mm ± 0.2 mm (4.50 mm – 4.90 mm)	20 tablets
5	Friability	NMT 1.0 % w/w	20 tablets
6	Disintegration time	NMT 15 minutes	6 tablets
7	Individual weight variation	640 mg ± 4%(614.00 mg – 666.00 mg)	20 tablets
8	Group weight variation	12.800g ± 2.0 % (12.540 g ± 13.060 g)	20 tablets

1. Compression machine was set at lower and high thickness and samples were collected for dissolution.
2. After sampling, compression was carried out at optimum thickness.
3. Compression machine at three different speeds between 10 – 30 RPM (15, 20 & 25 RPM) of turret and samples were collected for Dissolution and Content uniformity testing at each speed. Also physical parameters at each speed were done.

4.9.7. HOPPER STUDY

To evaluate the effect of vibration during compression on blend uniformity, hopper study was carried out at maximum speed of the machine. Filling the hopper completely and compression machine was run. Tablets were collected when powder level in the hopper is full, approximately middle of the hopper and when it is near the end of the hopper. The collected samples were tested for uniformity of content and physical parameters.

4.9.8. COATING

Coating was carried as per BMR. Before starting coating, average weight of core tablets was recorded. After coating process the appearance and weight gain during coating was tested. After completion of coating check for Description, Weight variation of 20 tablets, LOD and Weight buildup.

4.9.8.1. CONDITIONS TO BE FULFILLED DURING COATING PROCESS

1. After loading the pan with tablets, it is rotated for 1 minute for dedusting and pre heating of tablets.
2. Inlet air temperature: **50 - 60** ^{o}C
3. Outlet air temperature: **45 - 50** ^{o}C
4. Atomization air pressure: **3.0 - 5.0** kg/cm^2
5. Pan RPM: **2 - 3**
6. Spray gun distance: **20 - 26** cm
7. Spray rate: **40 - 60** ml/gun/min

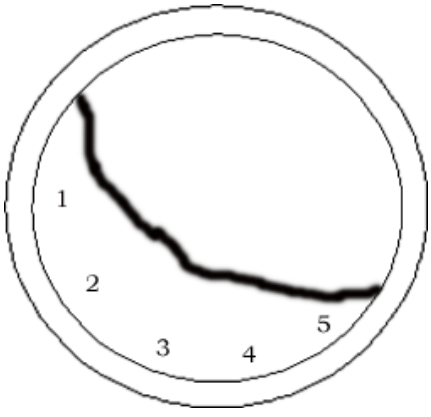


Fig.7 Sampling Locations for Coating Pan

4.9.8.2. DISSOLUTION PROFILE

Dissolution was carried out after compression, coating and for finished product. The samples are taken from the pooled samples.

Specifications for Dissolution

- Apparatus : IP – I
- RPM : 100
- Medium : 900 ml of a 4.0 per cent w/v solution of *sodium lauryl sulphate*(Degassed)
- Temperature : $37^{o}C \pm 0.5^{o}C$
- Sample Size : 6 Tablets
- Absorbance : 291 nm
- Time interval : 60 minutes
- Limit : NLT 70 % of stated amount

4.9.9. PACKING

Packing of Griseofulvin tablets include both primary and secondary packing. Blister packing is the primary packing and the process of primary packing involves the following steps:

Forming, Feeding, Sealing, Printing, Punching/Cutting.

4.9.9.1. Blister Packing

Packing was done as per Batch Packing Record. Before starting packing operations, the sealing roller temperature and forming roller temperature and speed of the machine were checked. After packing, blister quality, blister appearance, proper sealing, leak test and impurities were tested. The process of secondary packing involves checking the blisters, Counting, Cartoning, Stickering, Carton weighing, Shippering, and shipper weighing.

4.9.10. STABILITY STUDIES

A drug substance should be evaluated under storage conditions (should be sufficient to cover storage, shipment, and subsequent use). The long term testing should cover a minimum of 12 month's duration for at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period.

Intended storage conditions as per ICH guidelines

TABLE: NO. 25

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

5. RESULTS

5.1. RESULTS FOR EQUPMENT QUALIFICATION

Observation

All the equipments have been tested for their Installation, Operational and Performance Qualification. The results were present within the specified IH limits.

Conclusion

Based on the report, validation of the Instrument qualification was concluded to be successful. The qualified equipments were used for the manufacturing of Griseofulvin tablets.

5.2. RESULTS FOR RAW MATERIALS

TABLE: NO. 26

Griseofulvin (IP)					
S.No	**Test Performed**	**IP Specifications**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	white powder	complies	complies	complies
2	Solubility	Freely soluble in *dimethyl formamide* and in *1,1,2,2-tetrachloroethane;* soluble in *acetone* and in *chloroform;* slightly soluble in *ethanol (95 per cent)* and in methanol; practically insoluble in *water*.	complies	complies	complies
3	Identification				
4	I)IR	Method A	complies	complies	complies
	II)Chemical test	Method B	complies	complies	complies
5	Melting point	217 - 224 ^{o}C	218.4 ^{o}C	218.0 ^{o}C	218.2 ^{o}C
6	appearance of solution	Test solution not more intensely coloured than reference solution	complies	complies	complies
7	Acidity	Not more than 1.0 ml of 0.2M NaOH is required to change the colour of test solution.	complies	complies	complies
8	specific optical rotation	+352° to +364°	361^{o}	362 ^{o}	363 ^{o}
9	Related substances (dechloro Griseofulvin, dehydro Griseofulvin)	Detected by GC	complies	complies	complies
10	heavy metals	NMT 20 ppm	< 20 ppm	< 20 ppm	< 20 ppm
11	matter soluble in light petroleum	NMT 0.2 %	0.2%	0.1%	0.2%
12	sulphated ash	NMT 0.2 %	0.1%	0.1%	0.05%
13	LOD	NMT 1.0 %	0.1%	0.1%	0.08%
14	Assay	NLT 97.0 % and NMT 102.0 %	98.8 %w/w	99.4 %w/w	100.1 %w/w

TABLE: NO. 27

Povidone IP					
S.No	**Test Performed**	**IP Specification**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	White hygroscopic powder	complies	complies	complies
2	Solubility	Freely soluble in *water*, in *chloroform* and in *ethanol 95%*. practically insoluble in *ether*	complies	complies	complies
3	Odour	Odourless	complies	complies	complies
4	Identification				
	I)IR	Test A	complies	complies	complies
	II)Chemical test	Test D	complies	complies	complies
5	Clarity and colour of solution	Solution A is clear, not more intensely coloured than *reference solution*	complies	complies	complies
6	Heavy metals	NMT 10 ppm	complies	complies	complies
7	Aldehydes	NMT 9.1 ml of 0.1M NaOH	complies	complies	complies
8	Vinyl pyrrolidone	NMT 3.6 ml of 0.05M Iodine	complies	complies	complies
9	Sulphated ash	NMT 0.1%	0.05%	100.05%	200.05%
10	Water	NMT 5.0%	4.1 %w/w	4.1 %w/w	4.1 %w/w

TABLE: NO. 28

Sodium lauryl sulphate					
S.No	**Test Performed**	**IP Specification**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	white powder	complies	complies	complies
2	Solubility	Freely soluble in *water*, forming an opalescent solution; partly soluble in *ethanol (95%)*.	complies	complies	complies
3	Identification tests				
	I)Foam test	Test A	complies	complies	complies
	II) Chemical test	Test B & C	complies	complies	complies
	III)Sodium salts	Test D	complies	complies	complies
4	Alkalinity	NMT 0.5 ml of 0.1M HCl	complies	complies	complies
5	Non-Esterified alcohols	NMT 4%	0.30%	0.30%	0.30%
6	Sodium chloride and sodium sulphate	NMT 8.0%	4.00%	4.00%	4.00%
7	Assay	NLT 85.0 %	98.7 %w/w	98.7 %w/w	98.7 %w/w

TABLE: NO. 29

Hypromellose USP					
S.No	**Test Performed**		**PVG01**	**PVG02**	**PVG03**
1	Appearance	white fibrous powder	white fibrous powder	white fibrous powder	white fibrous powder
2	identification				
	I)chemical test	Method A, B, C	complies	complies	complies
3	viscosity		5.8 cps	5.7 cps	5.7 cps
4	LOD	NMT 5.0 %	2.20%	3.30%	3.30%
5	residue on ignition	NMT 1.5 %	0.50%	0.50%	0.50%
6	heavy metals	NMT 20 ppm	complies	complies	complies
7	assay(Methoxy content)	28-30 %	28.30%	28.30%	28.30%
8	assay (Hydroxypropoxy content)	7-12 %	9.10%	8.90%	8.90%
9	particle size		100	100	100
10	pH	5-8	7.1	7.29	7.29
11	chlorides	NMT 0.5 %	< 0.5 %	< 0.5 %	< 0.5 %

TABLE: NO. 30

Dichloromethane					
S.No	**Test Performed**	**BP Specification**	**PVG01**	**PVG02**	**PVG03**
1	appearance	A clear, colourless, volatile liquid	complies	complies	complies
2	solubility	Sparingly soluble in water, miscible with ethanol(96%).	complies	complies	complies
3	identification				
	I)IR	Sample spectrum compared with standard	complies	complies	complies
	II)Refractive index	1.423 – 1.425	1.423	1.423	1.423
4	acidity	NMT 0.15 ml of 0.1M NaOH	0.1 ml	0.1 ml	0.1 ml
5	relative density	1.320 – 1.332	1.323	1.323	1.323
6	heavy metals	NMT 1.0 ppm	complies	complies	complies
7	free chlorine	No blue colour with KI and Starch	complies	complies	complies
8	residue on evaporation	NMT 1.0 g	0.1 mg	0.1 mg	0.1 mg
9	water	NMT 0.05 %m/m	0.006%m/m	0.006%m/m	0.006%m/m

TABLE: NO. 31

Isopropyl alcohol					
S.No	**Test Performed**	**IP Specification**	**PVG01**	**PVG02**	**PVG03**
1	appearance	clear colourless liquid	complies	complies	complies
2	odour	characteristic and spirituous	complies	complies	complies
3	solubility	Miscible with *water,* with *chloroform* and with *ether.*	complies	complies	complies
4	Identification test				
	I)chemical test	Test A	complies	complies	complies
	II)chemical test	Test B	complies	complies	complies
5	acidity or alkalinity	NMT 0.06 ml of 0.1M NaOH	complies	complies	complies
6	distillation range	Not less than 95.0% v/v	97.40%	97.40%	97.40%
7	refractive index	Between 1.377 and 1.378	1.377	1.377	1.377
8	weight/ml	Between 0.782 and 0.786 g	0.783 g/ml	0.783 g/ml	0.783 g/ml
9	Aldehydes and ketones	NMT 2.0 ml of 0.1M NaOH	complies	complies	complies
10	benzene and related substances	Determined by GC	NOT DETECTED	NOT DETECTED	NOT DETECTED
11	non volatile matter	Not more than 0.002% w/v	0.0006 %w/v	0.0006 %w/v	0.0006 %w/v
12	water insoluble matter	Mix 1 volume with 19 volumes of *water;* no opalescence is produced.	complies	complies	complies
13	water	Not more than 0.50% w/w	0.07 %w/w	0.07 %w/w	0.07 %w/w

TABLE: NO. 32

Glycerin IP					
S.No	**Test Performed**	**IP Specification**	**PVG01**	**PVG02**	**PVG03**
1	appearance	Clear colourless, odourless, syrupy liquid	Complies	complies	complies
2	Identification				
	I)IR		complies	complies	complies
	II)Refractive index	Test A	1.472	2.472	3.472
3	water content	Not more than 2.0% w/w	0.3 %w/w	0.3 %w/w	0.3 %w/w
4	assay	NLT 98.0 % and NMT 101.0 %	99.6 % w/w	99.6 % w/w	99.6 % w/w

TABLE: NO. 33

Colloidal silicone dioxide IP					
S.No	**Batch No**	**IP SPECIFICATIONS**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	light, fine , White, Amorphous powder	Complies	Complies	Complies
2	Solubility	Practically insoluble in *water* and in *mineral acids* with the exception of *hydrofluoric acid.* Dissolves in hot solutions of *alkali hydroxides*. When 1 g is shaken vigorously with 20 ml of *carbon tetrachloride* for 3 minutes; a transparent gel is produced.	complies	complies	complies
3	Identification				
	I)Test for Silicates	Gives the reaction for Silicates	complies	complies	complies
4	pH	3.5 – 5.5	4.2	4.6	4.2
5	chlorides	NMT 250 ppm	complies	complies	complies
6	arsenic	NMT 8 ppm	complies	complies	complies
7	Heavy metals	NMT 25 ppm	complies	complies	complies
8	loss on ignition	NMT 5.0 %	2.20%	2.30%	2.20%
9	Assay	NLT 99.0 % and NMT 100.5 %	100.00%	99.90%	100.00%

TABLE: NO. 34

Starch IP					
S.No	**Batch No**	**IP SPECIFICATIONS**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	Very fine, white or slightly yellowish powder which are readily reducible to powder, creaks when pressed between the fingers	complies	complies	complies
2	Odour	Odourless	complies	complies	complies
3	Solubility	Practically insoluble in cold *water* and in *ethanol (95%)*	complies	complies	complies
4	Identification				
	I)Microscopy II)Chemical test	Method A & B	complies	complies	complies
5	Acidity	NMT 2.0 ml	complies	complies	complies
6	Iron	NMT 40 ppm	complies	complies	complies
7	Florescence	No fluorescence	complies	complies	complies
8	Oxidizing substances	no distinct brown or blue colour is observed.	complies	complies	complies
	Microbial limits				
	I)Total aerobic count	NMT 10 cfu/g	< 10 CFU/G	< 10 CFU/G	< 10 CFU/G
9	II)Pathogens E.coli & Salmonella	Negative	Absent	Absent	Absent
10	Sulphated ash	NMT 0.6 %	0.06%	0.06%	0.06%
11	Loss on drying	NMT 15 % w/w	7.1 % w/w	7.1 % w/w	7.1 % w/w

TABLE: NO. 35

Sodium starch glycollate IP					
S.No	**Batch No**	**IP SPECIFICATIONS**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	Very fine, white or off-white, free-flowing powder	Complies	Complies	Complies
2	Solubility	Practically insoluble in *water*; insoluble in most organic solvents	Complies	complies	complies
3	Odour	Odourless	Complies	complies	complies
4	Identification				
	I) IR	Method A	Complies	complies	complies
	II) Chemical test (Iodine)	Method B	Complies	complies	complies
	III) Chemical test (for Sodium)	Method C	Complies	complies	complies
5	pH	5.5 – 7.5	6.146	6.146	6.146
6	heavy metals	NMT 20 ppm	< 20 ppm	< 20 ppm	< 20 ppm
7	iron	NMT 20 ppm	< 20 ppm	< 20 ppm	< 20 ppm
8	sodium chloride	NMT 10.0 %	5.6%	5.6%	5.6%
10	microbial contamination				
	I)total bacterial count	NMT 10 cgu/g	< 10 CFU/G	< 10 CFU/G	< 10 CFU/G
	II) pathogens E.coli & Salmonella	Negative	Absent	Absent	Absent
11	LOD	NMT 10.0 %	7.5 % w/w	7.5 % w/w	7.5 % w/w
12	Assay	NLT 2.8 % - NMT 4.5 % of Na	3.70%	3.70%	3.70%
13	Bulk density	IH	0.72 g/ml	0.72 g/ml	0.72 g/ml
14	True density	IH	0.91 g/ml	0.91 g/ml	0.91 g/ml
15	Finess % retained on #200	IH	0%	0%	0%

TABLE: NO. 36

Magnesium stearate IP					
S.No	**Batch No**	**IP SPECIFICATIONS**	**PVG01**	**PVG02**	**PVG03**
1	Appearance	Very fine, light, white powder; unctuous and free from grittiness.	Complies	Complies	Complies
2	Solubility	Practically insoluble in *water*, in *ethanol* and in *ether*	Complies	complies	complies
3	Odour	odourless	complies	complies	complies
4	Identification				
	I)Freezing point	NLT 53 ^{o}C	56 ^{o}C	56 ^{o}C	56 ^{o}C
5	Appearance of solution	Test solution not more intensely coloured than *reference solution*	complies	complies	complies
6	Appearance of solution of fatty acids	Test solution not more intensely coloured than *reference solution*	complies	complies	complies
7	Acidity and alkalinity	NMT 0.05 ml of *0.1 M HCl* or 0.1 M NaOH is required to change the colour of the solution.	complies	complies	complies
8	Acid value of fatty acids	195-210	200	200	200
9	Free stearic acid	NMT 3.0 %	1.40%	1.40%	1.40%
10	Zinc stearate	no violet precipitate is formed.	complies	complies	complies
11	Heavy metals	NMT 20 ppm	< 20 ppm	< 20 ppm	< 20 ppm
12	Chlorides	NMT 250 ppm	< 250 ppm	< 250 ppm	< 250 ppm
13	sulphates	NMT 0.6 %	< 0.6 %	< 0.6 %	< 0.6 %
14	LOD	6.0 %	4.5 %w/w	4.5 %w/w	4.5 %w/w
15	Assay	NLT 3.8 % and NMT 5.0 %	4.6 %w/w	4.6 %w/w	4.6 %w/w
16	Microbial limits				
	i) Total aerobic microbial count	NMT 10 cfu/g	< 10 CFU/G	< 10 CFU/G	< 10 CFU/G
	ii)pathogens(E.coli, salmonella,P.Aeruginosa,S.aureus)	Negative	Absent	Absent	Absent

TABLE: NO. 37

Talc IP					
S.No	Batch No	IP SPECIFICATIONS	PVG01	PVG02	PVG03
1	Appearance	A white or almost white powder, free from grittiness; readily adheres to the skin; unctuous to the touch; odourless.	complies	complies	complies
2	Solubility	Practically insoluble in *water* and in dilute solutions of acids and alkali hydroxides	complies	complies	complies
3	Identification				
	I)microscopy	Method A	complies	complies	complies
	II) Chemical test	Method B	complies	complies	complies
	III) Chemical test	Method C	complies	complies	complies
4	acidity/ alkalinity	not more than 0.3 ml of *0.1M HCl*	complies	complies	complies
5	iron	NMT 10 ppm	complies	complies	complies
6	acid soluble substances	NMT 2.0 %	0.2%	0.7%	0.2%
7	water soluble substances	NMT 10 mg	0.0001%	0.1000%	0.0001%
8	carbonates	No effervescence	complies	complies	complies
9	chlorides	NMT 250 ppm	complies	complies	complies
10	organic compounds	Residue NMT slightly yellow	complies	complies	complies
11	LOD	NMT 1.0 %	0.12 % w/w	0.2 % w/w	0.12 % w/w
12	Microbial limits				
	I)Total viable aerobic count	NMT 10 cfu/g	< 10 CFU/G	< 10 CFU/G	< 10 CFU/G

TABLE: NO. 38

Purified Water					
S.No	**Batch No**	**IP SPECIFICATIONS**	**PVG01**	**PVG02**	**PVG03**
1	appearance	Clear, colourless liquid; odourless and tasteless.	Complies	complies	complies
2	Acidity or Alkalinity	Negative	Complies	complies	complies
3	Ammonium	Water with alkaline potassium mercuric-iodide solution is not more intensely coloured than the standard solution	Complies	Complies	Complies
4	Calcium and Magnesium	A pale blue colour is produced with ammonia buffer, mordant black II and Disodium edetate	Complies	Complies	Complies
5	Heavy metals	(NMT 0.1 ppm)	complies	complies	complies
6	Chloride	The appearance of the solution not changed for 15 minutes	Complies	Complies	Complies
7	Nitrate	(NMT 0.2 ppm)	complies	complies	complies
8	Sulphate	The appearance of the solution not changed for one hour	Complies	Complies	Complies
9	Oxidisable substances	The solution remained faintly pink	Complies	Complies	Complies
10	Residue on evaporation	NMT 0.001 %	0.0002%	0.0002%	0.0002%
11	pH	(5 – 7)	6.27	6.17	6.31
12	Ammonia	Yellow colour produced immediately is not darker than that of standard solution	Complies	Complies	Complies
13	CO2	The mixture remained clear	Complies	Complies	Complies
15	Total Microbial Count	Negative	complies	complies	complies
16	Test for pathogens	Negative	complies	complies	complies
17	Microbial Limit	(NMT 100 cfu/ml)	complies	complies	complies

Observation

All the raw materials have been tested for their purity and Quality as per the specifications and the results were present within the specified IP limits and USP limits for Hypromellose, BP specifications for Dichloromethane

Conclusion

Based on the report, we can conclude the validation of Raw materials used in the manufacturing of Griseofulvin tablets as successful.

5.3. RESULTS FOR PROCESS VALIDATION

5.3.1. DRY MIXING

Fixed Parameters

RMG speed : Slow

Lot size : 120.96

Variables considered for study : Mixing time

Time interval studied : 5 minutes

Measured response : Content uniformity and RSD

Acceptance criteria : 100 ± 15 % (RSD NMT 6.0%)

Batch taken for study : GRIS01, GRIS02, GRIS03.

5.3.1.1. The Content Uniformity and RSD values after 5 minutes of dry mixing

TABLE: NO. 39

Dry mixing time	**5 Minutes**		
Batch No	**GRIS01**	**GRIS02**	**GRIS03**
Minimum	94.03	93.33	94.18
Maximum	98.12	100.23	99.18
Average	96.13	95.89	96.24
RSD	1.38	2.24	1.94

Observations:

It is observed from the compiled analytical data of the content uniformity and it's RSD after 5 minutes dry mix the values of the three batches are well within the acceptance criteria as per IH specifications. The distribution of Griseofulvin IP is well acceptable at 5 minutes of dry mixing as shown by the samples analyzed data. The results show closer homogeneity of drug distribution in the dry mix stage.

5.3.1.2. Dry mix pooled sample results of B. No GRIS01, GRIS02, GRIS03.

TABLE: NO. 40

S.No	Parameter	GRIS01	GRIS02	GRIS03
1	% retains on #100	0.0% w/w	0.0% w/w	0.0% w/w
2	Tapped density(g/ml)	0.446	0.435	0.426
3	Water Content (%w/w)	1.87	1.94	1.86

Observations:

Sieve analysis, water content and tapped density values of three batches are comparable and are in closer homogeneity as per IH specifications.

Conclusion:

The dry mixing time of 5 minutes is concluded as validated mixing time at fast speed.

5.3.2. GRANULATION

Fixed parameters

Lot size : 120.96 kg (dry basis)

Variables considered for study : Mixing time, Impeller reading, Chopper amperage.

Acceptance criteria : Physical appearance granules

Measured response : Impeller reading, Chopper amperage

Batch taken for study : GRIS01, GRIS02, GRIS03.

5.3.2.1. Impeller reading of RMG

TABLE: NO. 41

Lot No	Final reading of Impeller (Ampere)
I	1.8
II	2.0
III	1.9

Observations:

The above compilation data shows that uniform granules formation of all three batches was observed at the Impeller (Slow speed) amperage 1.8 – 2.0 amps as per BMR (IH specifications).

Conclusion:

The desired granular mass was obtained between impeller amperage 1.8-2.0 amps. Resultant granules after drying and milling have desired flow properties. All the three batches resulted in granules with desired flow and compaction, which is evident from data of compression tablets. Hence the granules stage of Griseofulvin 375 tablet is concluded as validated at impeller amperage of 1.8-2.0 amps.

5.3.3. DRYING

Fixed parameters

Lot size : 120.96kg

Variables considered for study : Drying time and Drying temperature

Measured response : LOD (loss on drying)

Acceptance criteria : < 1.0 %w/w

Batches taken for study : GRIS01 (Lot-I, Lot-II, Lot-III)

5.3.3.1. Inlet, Outlet, Product Temperatures and LOD Results

TABLE: NO. 42

Batch no	**Inlet temperature (^{o}C)**	**Outlet temperature (^{o}C)**	**Product temperature (^{o}C)**	**LOD (% w/w)**
VB001	48	23	23	0.81
VB002	48	23	23	0.82
VB003	47	22	21	0.79

Observation:

Drying was carried out as per BMR (IH specifications). During drying the desired LOD of < 1.0 % w/w was achieved at air drying for 8-25 minutes.

Conclusion:

According to observations during drying for all three batches, it was concluded that only air drying the granular material after granulation is required till the LOD is NMT 1.0%.

5.3.4. BLENDING

Fixed parameters

Blender RPM : Slow speed

Blender Load : 537.6kg

Variables considered for study : Blending time

Time interval studied : After 20, 25 & 30 (25+5) minutes

Measured response : Uniformity of content and RSD

Acceptance criteria : 100 ± 15 %(RSD NMT 6.0%)

Batches taken for study : GRIS01, GRIS02, GRIS03

5.3.4.1. The Content Uniformity of Griseofulvin and RSD values after blending

TABLE: NO. 43 Batch No: GRIS01

Blending time (Minutes)	20	25	30
Minimum	89.57	90.78	89.53
Maximum	102.41	98.48	99.5
Average	95.86	95.00	92.46
RSD	3.79	2.55	3.58

TABLE: NO. 44 Batch No: GRIS02

Blending time (Minutes)	20	25	30
Minimum	88.08	94.14	93.49
Maximum	98.72	100	100.39
Average	93.23	96.92	96.04
RSD	3.73	1.73	2.51

TABLE: NO. 45 Batch No: GRIS03

Blending time (Minutes)	20	25	30
Minimum	89.94	89.9	87.22
Maximum	99.29	98.29	100.29
Average	94.4	93.79	95.16
RSD	3.1	2.77	3.68

Observations

It is observed from the compiled analytical data of the uniformity of content and it is RSD in the blend that the values of all the three batches are well within the acceptance criteria as per IH specifications, when blended for 20 & 25 minutes. The Content uniformity results of Griseofulvin in the blend of Griseofulvin tablets after blending of all the three batches of GRIS01, GRIS02, and GRIS03.

5.3.4.2. Test Results for Blend

TABLE: NO. 46

S.No	Test Performed	GRIS01	GRIS02	GRIS03
1	Appearance	white granular powder	white granular powder	white granular powder
2	Identification			
	I) IR	Complies	complies	complies
	II)UV	Complies	complies	complies
	III)Chemical test	Complies	complies	complies
3	Assay	375.5 mg	375.5 mg	375.5 mg
4	Water content	1.90%	101.90%	201.90%
5	Bulk density	0.83 g/ml	0.84 g/ml	0.85 g/ml

Observation

The distribution of Griseofulvin IP is well acceptable at 25 minutes of blending and 5 minutes lubrication as shown by the samples analyzes. The results show closer homogeneity of drug distribution in the blend as per IH specifications.

5.3.4.3. Blend pooled sample results

TABLE: NO. 47

Parameters	Batch no		
	GRIS01	GRIS02	GRIS03
Sieve analysis (% w/w)			
% retains on # 20	33.40	18.90	41.10
% retains on # 40	68.00	67.30	77.30
% retains on # 60	78.20	82.70	82.90
% retains on # 80	82.50	85.70	85.10
% retains on # 100	85.80	87.20	87.70
Untapped density (g/ml)	0.76	0.74	0.73
Tapped density (g/ml)	0.86	0.87	0.85
Moisture content	2.28	2.15	1.50

Observation

Sieve analysis, untapped density, Tapped density and Moisture content results for the blend pooled samples were found to be within limits as per IH.

5.3.4.4. The Assay results of Blend as follows

TABLE: NO. 48

Batch no	**GRIS01**	**GRIS02**	**GRIS03**
Assay (mg) of Griseofulvin	98.47	99.86	98.66

Observation

Assay values of all three batches are comparable and are in closer homogeneity as per IH specifications.

Conclusion

The blending time of 30 minutes is concluded as validated blending time at slow speed of blender for Griseofulvin 375 blending, when the process is performed in 2000 litres capacity Octagonal blender for a batch size of 537.6 kg.

5.3.5. COMPRESSION

Fixed parameter

Number of station : 37 stations

Variables considered for study : Thickness, Compression speed, Hopper level

Speeds studied : 10–20 RPM

Batches taken for study : GRIS01, GRIS02, GRIS03

5.3.5.1. Response and Acceptance criteria during compression

TABLE: NO. 49

MEASURED RESPONSE	ACCEPTANCE CRITERIA
Appearance	White capsule shaped, uncoated tablets plain on both sides
Group weight variation	12.80 g ± 2% (12.540 - 13.060g)
Individual weight variation	640.00mg ± 4% (614.00mg - 666.00mg)
Thickness	4.70 ± 0.2mm (4.50 to 4.90mm)
Hardness	NLT 3.0 kg/cm²
Friability	NMT 1.0% w/w
Disintegration time	NMT 20 minutes

5.3.5.2.Dissolution values at different thickness

Limit: NLT 80 % in 45 Minutes

TABLE: NO. 50

% of Griseofulvin						
Batch No	**GRIS 01**		**GRIS 02**		**GRIS 03**	
Thickness	**Lower**	**Higher**	**Lower**	**Higher**	**Lower**	**Higher**
Minimum	90.42	90.47	86.62	90.18	90.38	93.66
Maximum	97.46	98.83	89.61	94.79	98.33	102.58
Average	92.71	93.45	87.83	93.16	94.54	96.59

Observation: Dissolution of tablets compressed at lower and higher thickness complies with IH specification.

5.3.5.3. Physical parameters of tablets compressed at different speeds of 10, 15 and 20 RPM for three batches (GRIS01, GRIS02 and GRIS03)

TABLE: NO. 51

Batch No: GRIS01

S.No	Parameter	Specification	10RPM	15RPM	20RPM
1	Appearance	white capsule shaped, uncoated tablets, plain on both sides	Complies	Complies	Complies
2	Group weight of 20 tablets	12.800 ± 2% (12.540 - 13.060 g)	12.788 - 12.826	12.782 - 12.816	12.792 - 12.852
3	Individual weight variation(mg)	640.0mg ± 4% (614.0 - 666.0mg)	625 - 655	628 - 656	629 – 659
4	Hardness (Kg/cm^2)	NLT 3.0 Kg/cm^2	8.25 - 10.36	8.90 - 10.50	9.20 - 10.62
5	Thickness (mm)	4.70 ± 0.2mm (4.50 - 4.90mm)	4.65 - 4.79	4.65 - 4.81	4.65 - 4.80
6	Friability (%w/w)	NMT 1.0%	0.14 - 0.19	0.09 - 0.20	0.11 - 0.20
7	Disintegration time	NMT 20 minutes	9.22 - 9.45	9.24 - 9.38	9.28 - 9.38

TABLE: NO. 52 Batch No: GRIS02

S.No	Parameter	Specification	10RPM	15RPM	20RPM
1	Appearance	white capsule shaped, uncoated tablets, plain on both sides	Complies	Complies	Complies
2	Group weight of 20 tablets	12.800 ± 2% (12.540 - 13.060 g)	12.805-12.825	12.803 - 12.835	12.805 - 12.836
3	Individual weight variation(mg)	640.0mg ± 4% (614.0 - 666.0mg)	629 - 660	630 - 660	629 - 662
4	Hardness (Kg/cm^2)	NLT 3.0 Kg/cm^2	9.20 - 12.68	9.50 - 12.55	9.86 - 12.96
5	Thickness (mm)	4.70 ± 0.2mm (4.50 - 4.90mm)	4.60 - 4.81	4.62 - 4.78	4.65 - 4.78
6	Friability (%w/w)	NMT 1.0%	0.17 - 0.26	0.13 - 0.20	0.13 - 0.20
7	Disintegration time	NMT 20 minutes	9.10 - 9.25	10.18 - 10.58	10.08 - 10.38

TABLE: NO. 53 Batch No: GRIS03

S.No	Parameter	Specification	10RPM	15RPM	20RPM
1	Appearance	white capsule shaped, uncoated tablets, plain on both sides	Complies	Complies	Complies
2	Group weight of 20 tablets	12.800 ± 2% (12.540 - 13.060 g)	12.798 - 12.820	12.798 - 12.855	12.806 - 12.856
3	Individual weight variation(mg)	640.0mg ± 4% (614.0 - 666.0mg)	628 - 660	630 - 660	630 – 662
4	Hardness (Kg/cm^2)	NLT 3.0 Kg/cm^2	10.11 - 13.12	10.98 – 12.88	10.20 - 12.45
5	Thickness (mm)	4.70 ± 0.2mm (4.50 - 4.90mm)	4.65 - 4.78	4.64 - 4.80	4.64 - 4.78
6	Friability (%w/w)	NMT 1.0%	0.13 - 0.16	0.17 - 0.20	0.17 - 0.20
7	Disintegration time	NMT 20 minutes	10.18 – 10.24	10.18 – 10.28	9.22 – 9.58

5.3.5.4. Dissolution of Griseofulvin tablets at different speeds for three batches

Limit: NLT 80 % in 45 Minutes

TABLE: NO. 54 Batch No: GRIS01

RPM	**10**	**15**	**20**
Minimum	93.11	90.09	91.86
Maximum	97.93	94.31	95.26
Average	96.13	92.70	93.66

TABLE: NO. 55 Batch No: GRIS02

RPM	**10**	**15**	**20**
Minimum	95.64	98.07	98.35
Maximum	102.03	103.08	101.44
Average	99.42	99.99	100.30

TABLE: NO. 56 Batch No: GRIS03

RPM	**10**	**15**	**20**
Minimum	90.84	90.39	91.86
Maximum	100.19	96.28	95.53
Average	94.88	93.24	93.74

5.3.5.5. Uniformity of content and RSD values of Griseofulvin in compressed tablets at different speeds for three batches.

TABLE: NO. 57 Batch No: GRIS01

RPM	**10**	**15**	**20**
Minimum	101.82	98.93	95.66
Maximum	105.62	110.86	107.64
Average	103.42	104.61	101.64
RSD	1.12	4.05	5.37

TABLE: NO. 58 Batch No: GRIS02

RPM	**10**	**15**	**20**
Minimum	94.47	97.39	97.08
Maximum	100.29	103.92	101.09
Average	98.03	101.61	99.83
RSD	1.84	1.67	1.09

TABLE: NO. 59 Batch No: GRIS03

RPM	**10**	**15**	**20**
Minimum	98.08	97.18	92.09
Maximum	106.67	101.62	98.95
Average	100.82	99.32	95.16
RSD	2.42	1.52	2.73

5.3.5.6. Assay values of Griseofulvin tablets at different speeds for three batches.

TABLE: NO. 60

Batch No	**GRIS01**	**GRIS02**	**GRIS03**
Griseofulvin IP	101.38	101.11	101.77

Observation:

All physical parameters, Dissolution, Uniformity of content and Assay of pool tablet values of Griseofulvin compressed tablets at different speeds are well within the limits and are complying with IH specification.

5.3.5.7. Physical parameters of Griseofulvin tablets compressed at different hopper levels for three batches

TABLE: NO. 61

Batch No GRIS01

S.No	parameter	Specification	FULL	MIDDLE	NEAR END
1	Individual weight variation(mg)	640.0mg ± 4% (614.0 - 666.0mg)	627 - 656	629 - 659	628 – 662
2	Thickness (mm)	4.70 ± 0.2mm (4.50 - 4.90mm)	4.65 - 4.80	4.65 - 4.80	4.62 - 4.79
3	Hardness (Kg/cm²)	NLT 3.0 Kg/cm²	9.58 - 10.12	9.65 – 9.75	9.58 - 10.21
4	Friability(%w/w)	NMT 1.0%	0.11	0.11	0.11
5	Disintegration time	NMT 20 minutes	9.28	9.36	9.32

TABLE: NO. 62

Batch No: GRIS02

S.No	parameter	Specification	FULL	MIDDLE	NEAR END
1	Individual weight variation(mg)	640.0mg ± 4% (614.0 - 666.0mg)	628 - 660	628 - 662	624 - 660
2	Thickness (mm)	4.70 ± 0.2mm (4.50 - 4.90mm)	4.62 - 4.76	4.62 - 4.77	4.62 - 4.78
3	Hardness (Kg/cm²)	NLT 3.0 Kg/cm²	11.30 - 12.66	11.55 - 12.96	10.58 - 12.82
4	Friability(%w/w)	NMT 1.0%	0.17	0.18	0.14
5	Disintegration time	NMT 20 minutes	9.36	9.32	9.35

TABLE: NO. 63

Batch No: GRIS03

S.No	parameter	Specification	FULL	MIDDLE	NEAR END
1	Individual weight variation(mg)	640.0mg ± 4% (614.0 - 666.0mg)	630 - 662	630 - 660	628 – 662
2	Thickness (mm)	4.70 ± 0.2mm (4.50 - 4.90mm)	4.64 - 4.78	4.65 - 4.78	4.65 - 4.78
3	Hardness (Kg/cm²)	NLT 3.0 Kg/cm²	10.20 - 11.86	10.25 - 11.86	09.58 - 11.75
4	Friability(%w/w)	NMT 1.0%	0.20	0.18	0.19
5	Disintegration time	NMT 20 minutes	9.32	9.48	9.42

5.3.5.8. Dissolution of Griseofulvin in compressed tablets at different levels of hopper (Full, Middle, near end) for three batches.

Limit: NLT 80 % in 45 Minutes

TABLE: NO. 64 FULL HOPPER

Batch No	GRIS01	GRIS02	GRIS03
Minimum	95.65	97.49	90.77
Maximum	98.79	101.20	94.67
Average	97.47	99.41	92.98

TABLE: NO. 65 MIDDLE HOPPER

Batch No	GRIS01	GRIS02	GRIS03
Minimum	91.38	92.99	92.32
Maximum	99.35	101.12	97.16
Average	94.10	96.20	94.79

TABLE: NO. 66 NEAR END HOPPER

Batch No	GRIS01	GRIS02	GRIS03
Minimum	90.68	93.27	92.30
Maximum	98.87	96.77	96.05
Average	95.16	94.56	94.17

Observation:

All physical parameters and dissolution values at different hopper level are well within the acceptance criteria and complying with the IH specification.

5.3.5.9. Uniformity of content values of Griseofulvin tablets at different levels of hopper (Full, Middle, Near end) for three batches.

TABLE: NO. 67 FULL HOPPER

Batch No	GRIS01	GRIS02	GRIS03
Minimum	95.38	96.39	93.30
Maximum	101.40	102.25	99.38
Average	98.36	100.24	95.73
RSD	1.66	1.89	2.41

TABLE: NO. 68 MIDDLE HOPPER

Batch No	GRIS01	GRIS02	GRIS03
Minimum	94.10	96.34	98.39
Maximum	99.81	103.22	105.54
Average	96.43	100.67	101.21
RSD	1.92	2.42	2.3

TABLE: NO. 69 NEAR END HOPPER

Batch No	GRIS01	GRIS02	GRIS03
Minimum	93.74	100.96	98.61
Maximum	100.97	108.22	102.06
Average	98.65	104.65	100.09
RSD	2.02	2.45	1.22

Observation:

All physical parameters and uniformity of content values at different hoper levels are well within the acceptance criteria and complying with the IH specification.

Conclusion:

According to the results observed, it was concluded that the compression process is validated and is under control for all the three batches of Griseofulvin tablets.

5.3.6. COATING

Fixed parameters : 537.6 Kg

Variables considered for study : Spray rate, Pan RPM, Peristaltic pump rate, Spray gun to tablet bed distance, Atomizing air pressure, inlet & outlet temperature.

Measured response : Dissolution profile and all tests as per current finished product IH Specification.

Acceptance criteria : As per current Finished product Specification.

Batches taken for study : GRIS01, GRIS02, GRIS03.

5.3.6.1. Coating parameters for three batches

TABLE: NO. 70

S.No	Parameter	Standard	Batch No		
			GRIS01	GRIS02	GRIS03
1	Inlet temperature	50 - 60 ^{o}C	60	60	59
2	Outlet temperature	45 - 50 ^{o}C	46	46	46
3	Atomization pressure	3.0 - 5.0 Kg/cm^2	3.0	5.0	5.0
4	Pan RPM	2 - 3	3	3	3
5	Spray gun distance (moving)	20 - 26 cm	23	24	23
6	Spray rate	40 - 60 ml/gun/min	53	52	52
7	Weight build up	Theoretical 6.66mg	6.72	7.03	6.84

5.3.6.2. Dissolution profile of Griseofulvin tablets for three batches Limit: NLT 70 % in 60 Minutes

TABLE: NO. 71 Batch No: GRIS01

Time interval (Minutes)	5	15	20	30	45
Minimum	17.50	58.38	68.95	86.60	88.59
Maximum	27.75	83.64	86.99	102.01	97.34
Average	21.42	70.36	76.84	93.44	92.01

TABLE: NO. 72 Batch No: GRIS02

Time interval (Minutes)	**5**	**15**	**20**	**30**	**45**
Minimum	31.15	77.13	89.26	92.21	96.73
Maximum	53.09	90.31	97.47	97.79	108.30
Average	38.47	85.44	92.18	95.07	99.33

TABLE: NO. 73 Batch No: GRIS03

Time interval (Minutes)	**5**	**15**	**20**	**30**	**45**
Minimum	22.18	72.22	84.17	89.31	92.23
Maximum	59.21	87.33	92.58	97.09	98.64
Average	37.81	82.21	89.84	91.72	94.15

Observation

Weight build up for all three batches observed was 1.08 to 2.50 mg per tablet. Dissolution profile of Griseofulvin tablets was observed within the specified IH limit. The coating process proved to be consistent among the batches. Therefore it was concluded that the coating process is validated.

Conclusion

According to the results observed, it was concluded that the compression process is validated and is under control for all the three batches of Griseofulvin tablets.

5.3.7. BLISTER PACKING

Fixed parameters

Blister forming temperature : 150 – 180^{o}C

Sealing temperature : 180 - 210^{o}C

Variables considered for study : Speed of the machine

Speeds studied : 30 – 40 cuts/minute

Measured Response : Blister quality, Leak test

Batches taken for study : GRIS01, GRIS02, GRIS03

Observation:

Blister packs comply with Leak test and Blister quality and were found to be satisfactory as per IH specifications at the speed of 30-40 cuts/minute and the specified forming and sealing temperatures.

Conclusion

At specified machine speed i.e. 25-40 cuts/minute and specified forming & sealing temperature, the blister packs formed comply with the specified limits mentioned in protocol and this speed is considered as validated.

5.3.7.1 Microbial activity study in Griseofulvin tablets for three batches

TABLE: NO. 74

Batch No	**IH Specification**	**GRIS01**	**GRIS02**	**GRIS03**
Total aerobic bacteria count	NMT 500 CFU/g	10 CFU/g	< 10CFU/g	< 10 CFU/g
Total aerobic yeast count	NMT 50 CFU/g	10 CFU/g	< 10CFU/g	< 10 CFU/g
Pathogens(P.aeruginosa, E.coli, S.aureus, Salmonella	Shall be absent	Absent	Absent	Absent

Observation

Microbial content of all three batches comply with the finished product specification.

Conclusion

From the above results obtained, it was concluded that the microbial activity was found to be absent.

5.3.1. YIELD RESULTS

TABLE: NO. 75

Stage	Batch No		
	GRIS01	**GRIS02**	**GRIS03**
Blending	99.91	99.93	99.91
Compression	98.29	98.22	97.72
Coating	97.61	97.50	97.08
Inspection	97.26	98.19	97.96
Packing	98.34	98.98	98.30

Conclusion

From the above results, it was concluded that the yields for all the three batches is satisfactory and within the specified limits.

5.3.2. FINISHED PRODUCT

TABLE: NO. 76

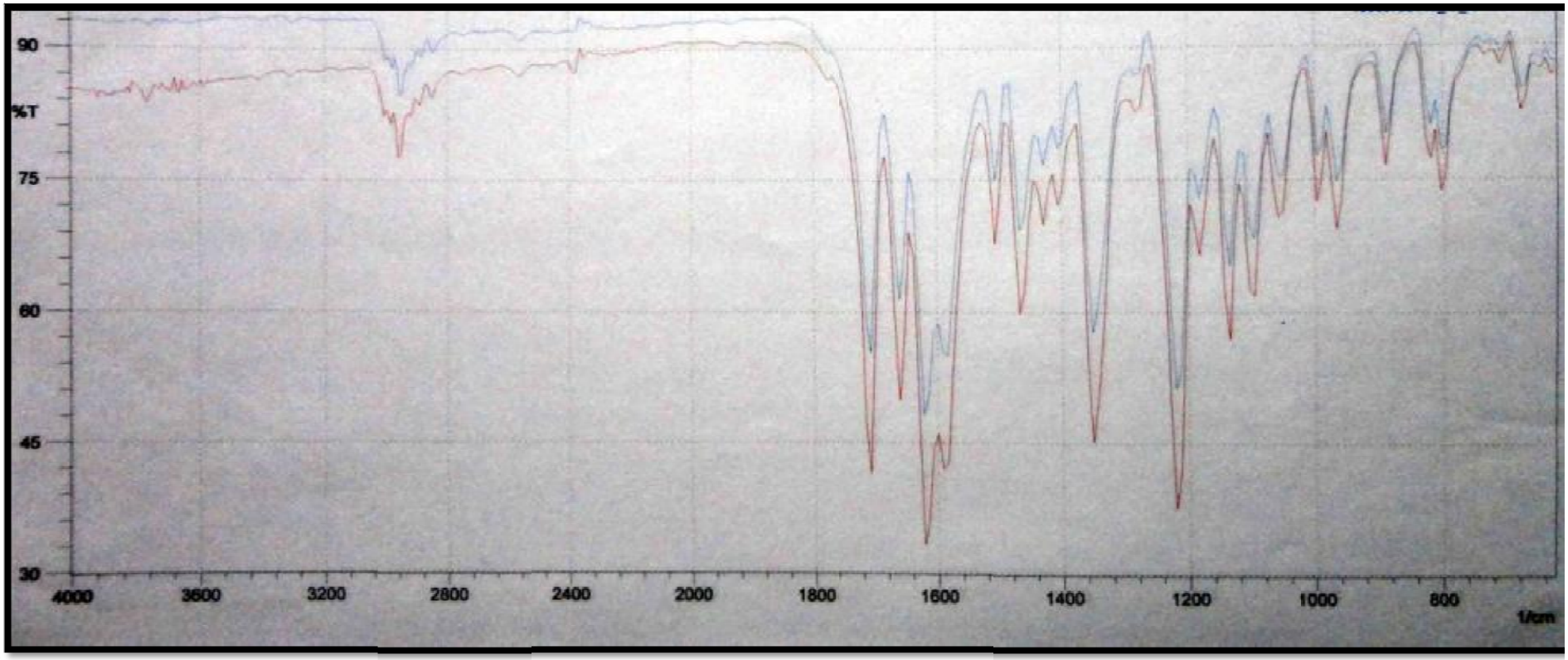
S.No	Test Performed	IH SPECIFICATIONS	GRIS01	GRIS02	GRIS03
1	Appearance	white to off-white film coated capsule shaped tablets	complies	complies	complies
2	Identification				
	i)IR	IR spectrum of sample was compared with Griseofulvin RS	complies	complies	complies
	ii)chemical test	As per IH specification	complies	complies	complies
3	Related substances	Determined by GC as per IH specification	complies	complies	complies
4	Dissolution	Limit: NLT 70 % in 60 Minutes	96.37	98.92	98.76
5	Uniformity of weight	12.80 g ± 2% (12.540 - 13.060g)	complies	complies	Complies
6	DT	NMT 20	9 min	10 min	11 min
7	Assay	IH specification	373.8 mg	373.8 mg	373.8 mg
8	Average weight	640.00mg ± 4% (614.00mg - 666.00mg)	647.017 mg	647.017 mg	647.017 mg
9	Thickness	4.70 ± 0.2mm (4.50 to 4.90mm)	4.58 mm	4.58 mm	4.58 mm
10	Hardness	NLT 3.0 kg/cm²	11.6 kg/cm2	11.6 kg/cm3	11.6 kg/cm4
11	Water content	IH specification	2.2 %w/w	2.2 %w/w	2.2 %w/w

Conclusion:

From the above results, we can conclude that the manufacturing process is in a state of control and capable of producing quality product uniformly.

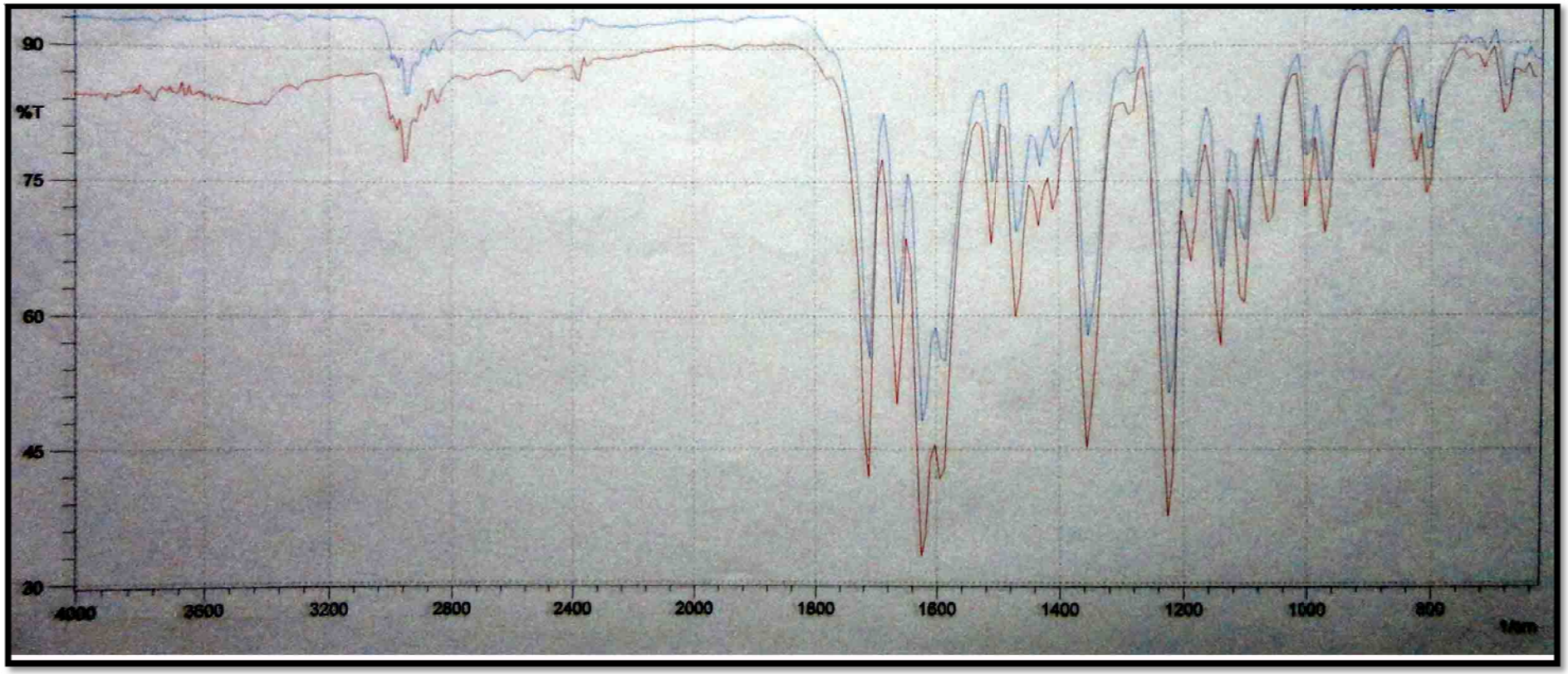
IR SPECTRAL ANALYSIS

The spectral analysis for the pure sample of Griseofulvin was performed to check the quality and purity of the raw materials used in the manufacturing of Griseofulvin tablets. The results for the IR spectral analysis are as follows:



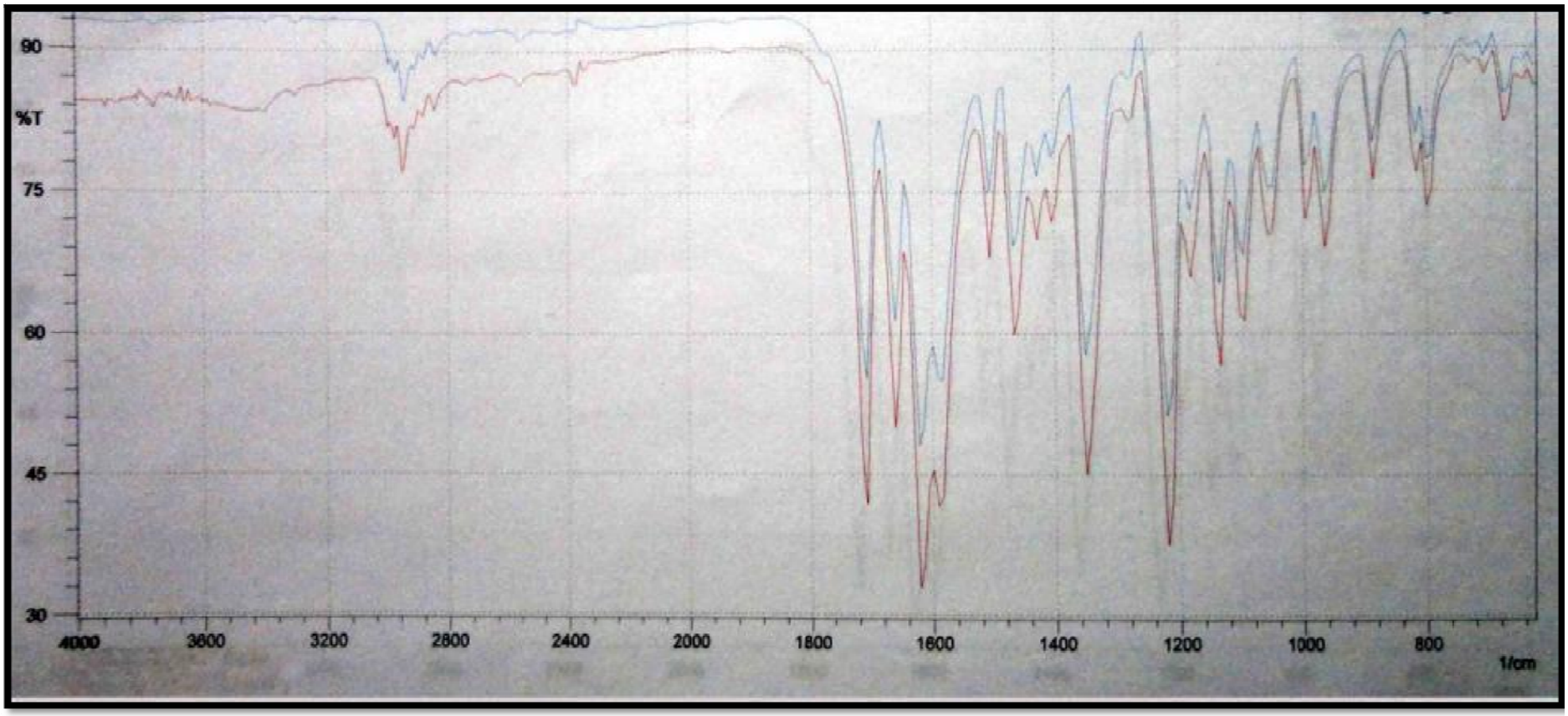
IR SPECTRUM OF GRISEOFULVIN - RM PVG01

Observation: The IR spectrum of Griseofulvin raw material was found to be identical with that of standard spectrum.



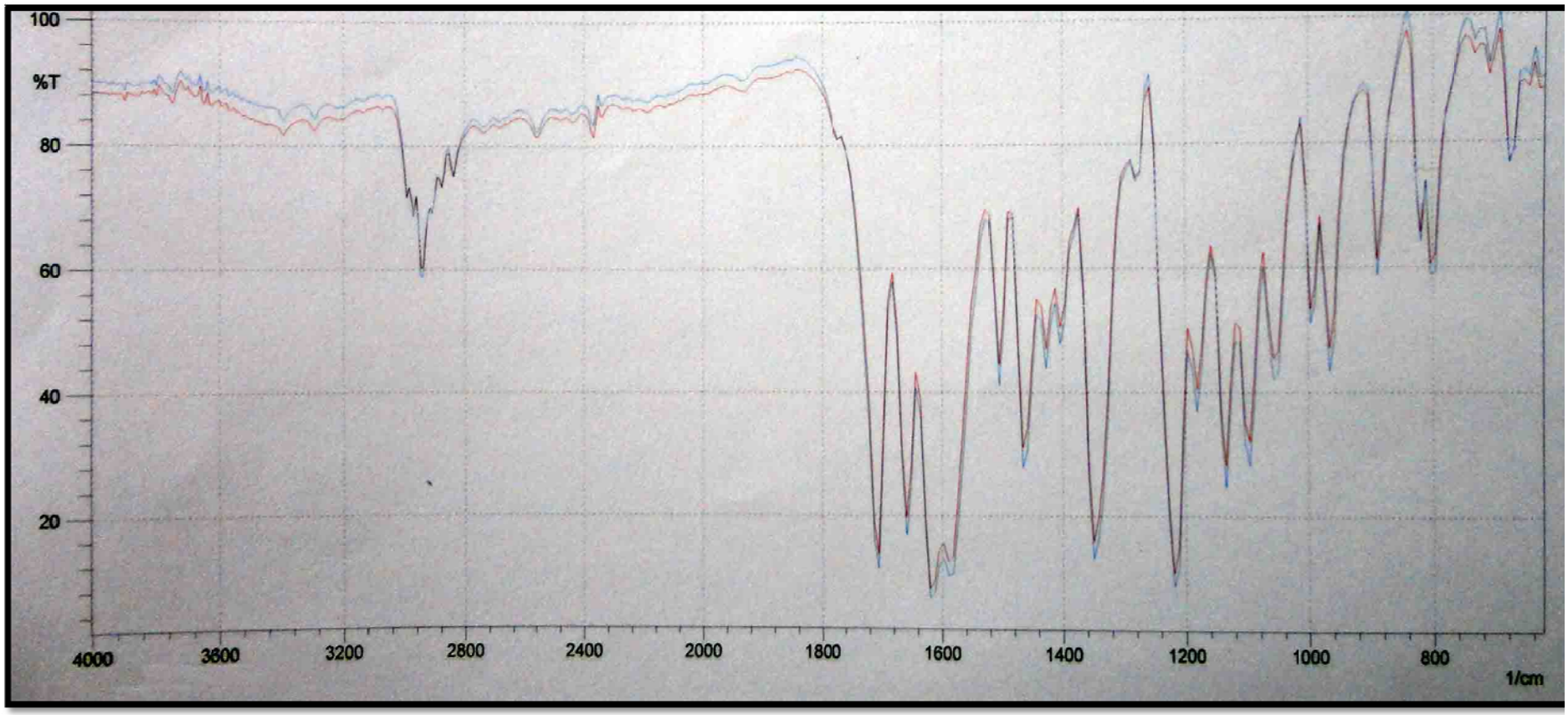
IR SPECTRUM OF GRISEOFULVIN - RM PVG02

Observation: The IR spectrum of Griseofulvin raw material was found to be identical with that of standard spectrum.



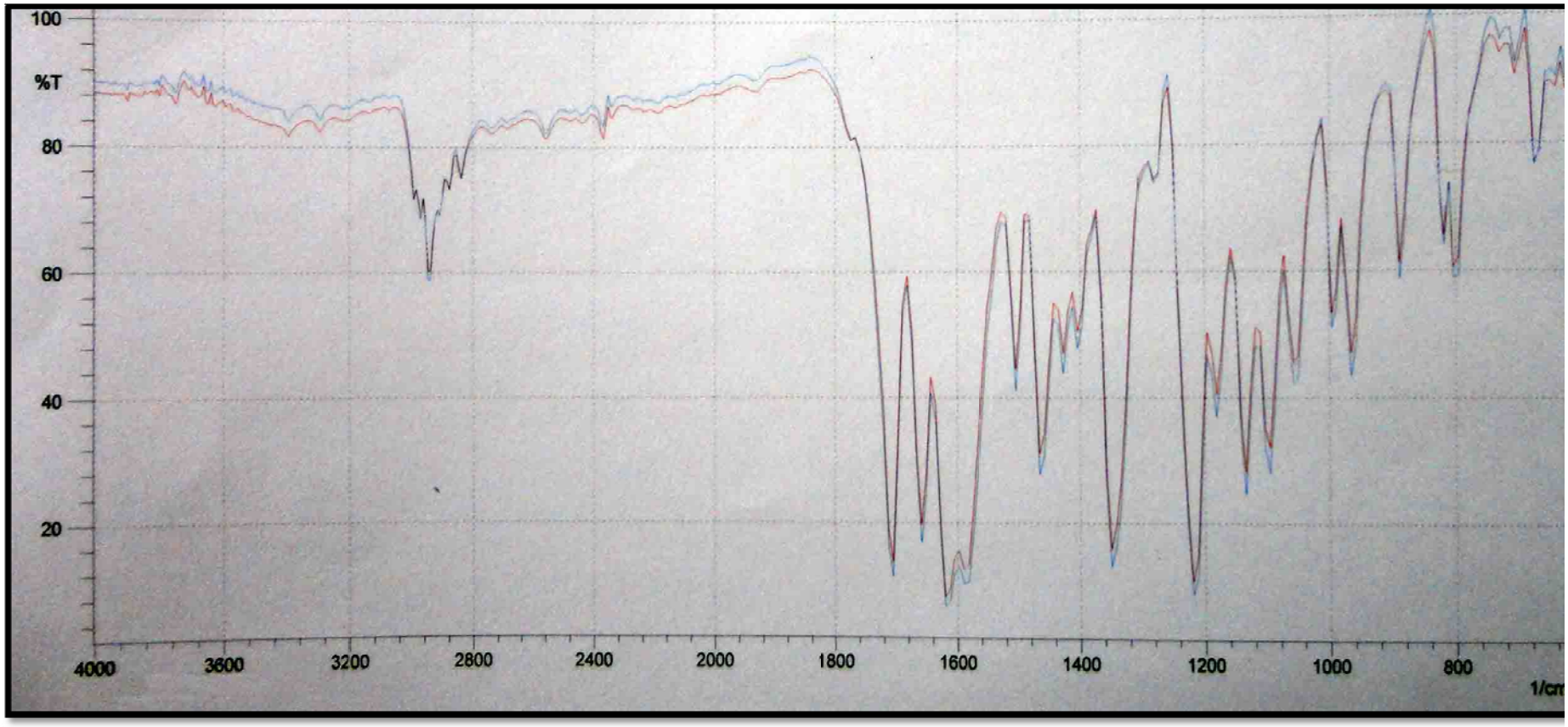
IR SPECTRUM OF GRISEOFULVIN - RM PVG03

Observation: The IR spectrum of Griseofulvin raw material was found to be identical with that of standard spectrum.



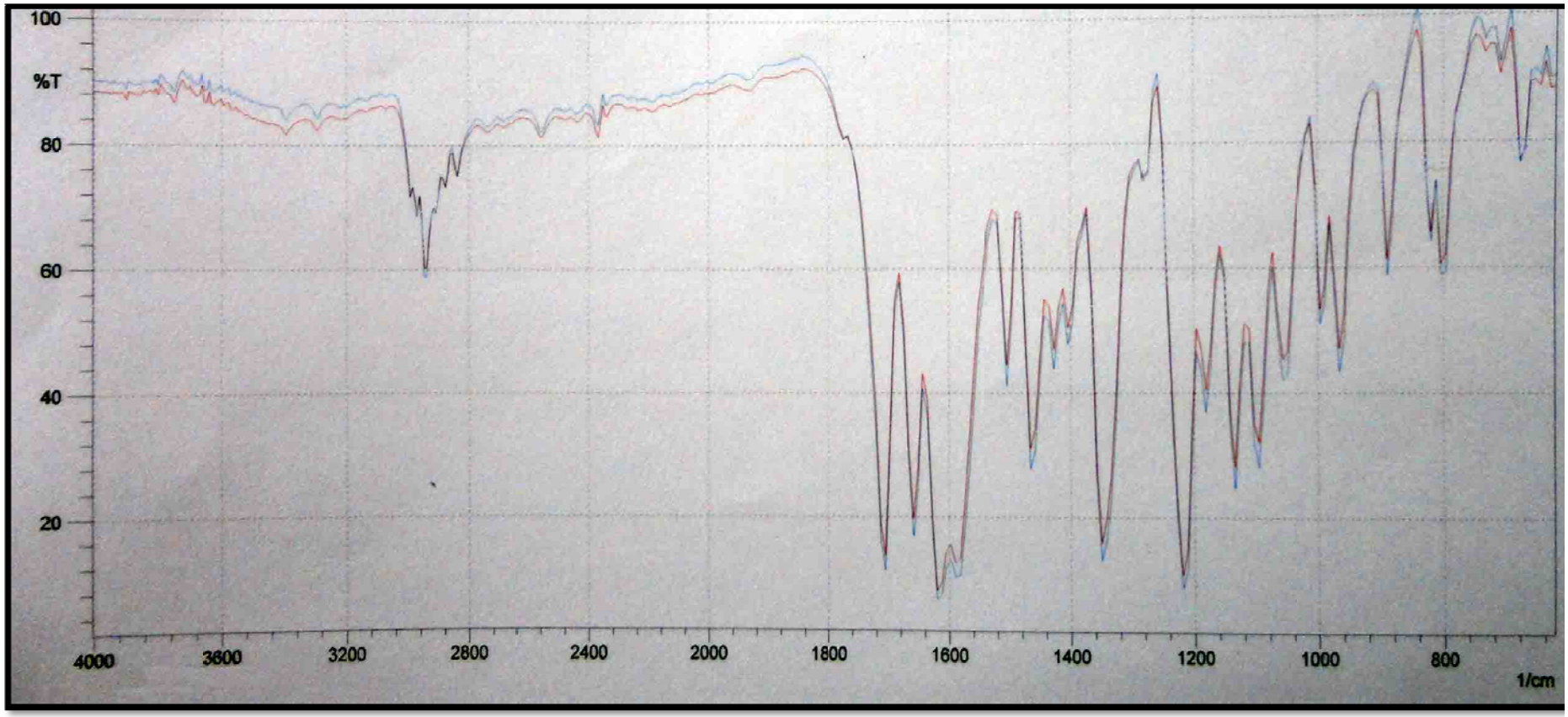
IR SPECTRUM OF GRISEOFULVIN FINISHED PRODUCT BATCH NO - GRIS01

Observation: The IR spectrum of Griseofulvin finished product was found to be identical with that of standard spectrum.



IR SPECTRUM OF GRISEOFULVIN FINISHED PRODUCT BATCH NO - GRIS02

Observation: The IR spectrum of Griseofulvin finished product was found to be identical with that of standard spectrum.



IR SPECTRUM OF GRISEOFULVIN FINISHED PRODUCT BATCH NO - GRIS03

Observation: The IR spectrum of Griseofulvin finished product was found to be identical with that of standard spectrum.

5.4.1. STABILITY REPORT FOR ALL THE THREE BATCHES STUDIED UNDER SPECIFIED CONDITIONS

TABLE: NO. 77 STABILITY REPORT FOR ALL THE THREE BATCHES STUDIED UNDER SPECIFIED CONDITIONS

Stability Study- GRIS01									
Label Claim: Each film coated tablet contain Griseofulvin IP									
Storage conditions: 40 ± 2 oC / 75 % ± 5 % RH (Accelerated Stability Studies)									
Shelf life: 36 Months									
S.no	Description	Average Weight	Disintegration time	Hardness	Water (% w/w)	Dissolution	Related substances	Assay	Microbial limits a.Bacteria b.Fungi C.Pathogens
Spec	Write off white film coated capsule shaped tablets	647.0 ± 2.5%(630. 83 mg and 663.18 mg)	NMT 30 min	NLT 2.5 kg/cm2	NMT 6.0 % w/w	NLT 70% in 60 min	complies	NLT 95% & NMT 105%	a.NMT 500 CFU/g b.NMT 50 CFU/g c.Shall be absent
Stage Initial	Complies	646.42	11	10.04 - 12.1	1.9	93.0 - 103.0	complies	99.4	complies
1M	Complies	649.13	9	9.04 - 11.39	2.4	98.14 - 102.12	complies	100.75	NA
2M	Complies	642.07	10	10.80 - 12.19	2.0	94.89 - 13.84	complies	100.04	NA
3M	Complies	643.36	10	10.97 - 12.76	1.6	87.63 - 91.62	complies	99.72	NA
6M	ON GOING STABILITY STUDY								

Observation: All the parameters are within the specified limits

TABLE: NO. 78

Stability Study- GRIS01									
Label Claim: Each film coated tablet contain Griseofulvin IP									
Storage conditions: 25 ± 2 oC / 60 % ± 5 % RH (Long-term storage condition)									
Shelf life: 36 Months									
S.no	Description	Average Weight	Disintegration time	Hardness	Water (% w/w)	Dissolution	Related substances	Assay	Microbial limits a.Bacteria b.Fungi C.Pathogens
Spec	Write off white film coated capsule shaped tablets	647.0 ± 2.5%(630.83 mg to 663.18 mg)	NMT 30 min	NLT 2.5 kg/cm2	NMT 6.0 % w/w	NLT 70% in 60 min	complies	NLT 95% & NMT 105%	a.NMT 500 CFU/g b.NMT 50 CFU/g c.Shall be absent
Stage Initial	Complies	646.42	11	9.23 - 12.18	1.9	93.00 – 103.00	complies	99.4	complies
3M	Complies	648.875	11	10.77 - 11.59	2.5	89.95 - 94.81	complies	100.33	NA
6 M	ON GOING STABILITY STUDY								
9 M									
12 M									
18 M									
24 M									
36 M									
48 M									

Observation: All the parameters are within the specified limits

TABLE: NO. 79

Stability Study- GRIS02									
Label Claim: Each film coated tablet contain Griseofulvin IP									
Storage conditions: 40 ± 2 oC / 75 % ± 5 % RH (Accelerated Stability Studies)									
Shelf life: 36 Months									
S.no	Description	Average Weight	Disintegration time	Hardness	Water (% w/w)	Dissolution	Related substances	Assay	Microbial limits a.Bacteria b.Fungi C.Pathogens
Spec	Write off white film coated capsule shaped tablets	647.0 ± 2.5%(630.83 mg and 663.18 mg)	NMT 30 min	NLT 2.5 kg/cm2	NMT 6.0 % w/w	NLT 70% in 60 min	complies	NLT 95% & NMT 105%	a.NMT 500 CFU/g b.NMT 50 CFU/g c.Shall be absent
Stage Initial	Complies	641.11	12	10.5 - 111.23	2.3	94.8	complies	100.4	complies
1M	Complies	652.61	12	10.09 - 11.11	1.8	96.72	complies	100.16	NA
2M	Complies	639.63	10	10.31 - 11.34	1.7	99.53	complies	99.19	NA
3M	Complies	649.63	11	6.08 - 7.23	1.6	99.02	complies	101.54	NA
6M	ON GOING STABILITY STUDY								

Observation: All the parameters are within the specified limits

TABLE: NO. 80

Stability Study- GRIS02									
Label Claim: Each film coated tablet contain Griseofulvin IP									
Storage conditions: 25 ± 2 oC / 60 % ± 5 % RH (Long-term storage condition)									
Shelf life: 36 Months									
S.no	Description	Average Weight	Disintegration time	Hardness	Water (% w/w)	Dissolution	Related substances	Assay	Microbial limits a.Bacteria b.Fungi C.Pathogens
Spec	Write off white film coated capsule shaped tablets	647.0 ± 2.5%(630.83 mg to 663.18 mg)	NMT 30 min	NLT 2.5 kg/cm2	NMT 6.0 % w/w	NLT 70% in 60 min	complies	NLT 95% & NMT 105%	a.NMT 500 CFU/g b.NMT 50 CFU/g c.Shall be absent
Stage Initial	Complies	639.54	12	7.5 – 10.23	1.8	95.20	complies	99.20	complies
3M	Complies	653.875	12	6.68 - 7.28	2.6	95.89	complies	101.28	NA
6 M	ON GOING STABILITY STUDY								
9 M									
12 M									
18 M									
24 M									
36 M									
48 M									

Observation: All the parameters are within the specified limits

TABLE: NO. 81

Stability Study- GRIS03									
Label Claim: Each film coated tablet contain Griseofulvin IP									
Storage conditions: 40 ± 2 oC / 75 % ± 5 % RH (Accelerated Stability Studies)									
Shelf life: 36 Months									
S.no	Description	Average Weight	Disintegration time	Hardness	Water (%w/w)	Dissolution	Related substances	Assay	Microbial limits a.Bacteria b.Fungi C.Pathogens
Spec	Write off white film coated capsule shaped tablets	647.0 ± 2.5%(630.83 mg and 663.18 mg)	NMT 30 min	NLT 2.5 kg/cm2	NMT 6.0 % w/w	NLT 70% in 60 min	complies	NLT 95% & NMT 105%	a.NMT 500 CFU/g b.NMT 50 CFU/g c.Shall be absent
Stage Initial	Complies	639.54	12	7.5 – 10.52	1.8	95.2	complies	99.2	complies
1M	Complies	642.24	12	10.40 - 11.56	2.3	98.31	complies	99.92	NA
2M	Complies	645.87	11	10.80 - 12.19	1.9	100.19	complies	100.13	NA
3M	Complies	648.97	13	9.84 - 10.19	2.5	98.88	complies	109.11	NA
6M	ON GOING STABILITY STUDY								

Observation: All the parameters are within the specified limits

TABLE: NO. 82

Stability Study- GRIS03									
Label Claim: Each film coated tablet contain Griseofulvin IP									
Storage conditions: 25 ± 2 oC / 60 % ± 5 % RH (Long-term storage condition)									
Shelf life: 36 Months									
S.no	Description	Average Weight	Disintegration time	Hardness	Water (% w/w)	Dissolution	Related substances	Assay	Microbial limits a.Bacteria b.Fungi C.Pathogens
Spec	Write off white film coated capsule shaped tablets	647.0 ± 2.5%(630.83 mg to 663.18 mg)	NMT 30 min	NLT 2.5 kg/cm2	NMT 6.0 % w/w	NLT 70% in 60 min	complies	NLT 95% & NMT 105%	a.NMT 500 CFU/g b.NMT 50 CFU/g c.Shall be absent
Stage Initial	Complies	639.54	12	7.57 - 9.34	1.8	95.2	complies	99.2	complies
3M	Complies	653.875	12	6.68 - 7.28	2.6	95.89	complies	101.28	NA
6 M	ON GOING STABILITY STUDY								
9 M									
12 M									
18 M									
24 M									
36 M									
48 M									

Observation: All the parameters are within the specified limits

6. DISCUSSION

The process validation of Griseofulvin 375 mg tablets for the batches GRIS01, GRIS02, GRIS03 was conducted for a batch size of 0.84 million tablets at Dry mixing, Blending, Compression, Coating and Packing stage.

DRY MIXING

The distribution of Griseofulvin IP is well acceptable at 5 minutes of dry mixing as shown by the samples analyzed data. The results show closer homogeneity of drug distribution in the dry mix stage as per IH specification. Sieve analysis, water content and tapped density values of three batches for dry mix pooled samples are comparable and are in closer homogeneity. Hence dry mixing time of 5 minutes at slow speed is concluded as validated dry mixing time for Griseofulvin 375mg tablets.

GRANULATION

The above compilation data shows that uniform granules formation of all three batches was observed at the Impeller (Slow speed) amperage 1.8 – 2.0 amps. The desired granular mass was obtained between impeller amperage 1.8-2.0 amps. Resultant granules after drying and milling have shown desired flow properties. In all the three batches desired flow and compaction is well observed, which is evident from data of compressed tablets. Hence the granules stage of Griseofulvin 375 tablet is concluded as validated at impeller amperage of 1.8-2.0 amps.

DRYING

Drying was carried out as per BMR (IH specification). During drying the desired LOD of < 1.0 % w/w was achieved at air drying for 8-25 minutes. It was concluded that only air drying the granular material after granulation is required till the LOD is NMT 1.0%. Hence the drying time of 8-25 minutes is concluded as validated.

BLENDING

The blending time of 30 minutes is concluded as validated blending time at slow speed of blender for Griseofulvin 375 blending, when the process is performed in 2000 liters capacity Octagonal blender for a batch size of 537.6 kg. The distribution of Griseofulvin is well acceptable at 25 minutes of blending and 5 minutes lubrication as shown by the samples analyzes. The results show closer homogeneity of drug distribution in the blend. Particle size distribution, Bulk density & Tapped density and Assay values of all three batches are

comparable and are in closer homogeneity. Hence the blending time 30 minutes as mentioned in the BMR (IH specification) stands validated.

COMPRESSION

The compression for all the three has been validated for different compression speed on 37-station compression machine. Entire compression was carried out in three different speeds. The physical parameters, results of dissolution and assay of the tablets compressed at different speeds of 10-20 RPM were well within the acceptable IH specified limits. The results are comparable among all the three runs. From the above it can be concluded that the Griseofulvin tablets of batch size 0.84 million tablets stands validated for compression speed range of 10-20 RPM on station compression machine.

COATING

The coating validated was performed for three consecutive batches. The weight buildup in tablets was measured and it is found within limits. It was concluded that the coating has to be performed with the parameters as mentioned in the BMR (IH specification) in order to obtain the desired buildup. The dissolution profile of all coated tablets of three batches is comparable. Finished product reports of all the three batches of GRIS01, GRIS02, and GRIS03 shows that final product meets the finished product specification.

BLISTER PACKING

At IH specified machine speed i.e. 25-40 cuts/minute and forming & sealing temperature, the blister packs formed comply with the specified IH limits for all the three batches of GRIS01, GRIS02, GRIS03 mentioned in protocol and this speed is considered as validated.

FINISHED PRODUCT

Finished product reports of all the three batches of GRIS01, GRIS02 & GRIS03 shows that final product meets the finished product IH specification.

STABILITY REPORT

The stability reports were present within the specified limits for all the three validation batches, GRIS01, GRIS02 & GRIS03 for long term and accelerated storage conditions. So the stability study was concluded to be validated.

7. SUMMARY AND CONCLUSION

1. All the raw materials used in the manufacturing of Griseofulvin 375mg Tablets, were tested as per the given specifications and the results were within the limits. Hence the validation of raw materials was concluded.
2. The equipment used in the manufacturing of the Griseofulvin 375mg Tablets were checked for their Installation, Operation and Performance Qualification and concluded.
3. The dry mixing time of 5 minutes is concluded as validated mixing time at fast speed.
4. The desired granular mass was obtained between impeller amperage 1.8-2.0 amps. Resultant granules after drying and milling have desired flow properties. All the three batches resulted in granules with desired flow and compaction, which is evident from data of compression tablets. Hence the granules stage of Griseofulvin 375 tablet is concluded as validated at impeller amperage of 1.8-2.0 amps.
5. According to observations during drying for all three batches, it was concluded that only air drying the granular material after granulation is required till the LOD is NMT 1.0%.
6. The blending time of 30 minutes is concluded as validated blending time at slow speed of blender for Griseofulvin 375 blending, when the process is performed in 2000 litres capacity Octagonal blender for a batch size of 537.6 kg.
7. From the dissolution profile it was concluded that the compression process was validated.
8. From the weight build up it was concluded that the validation of coating was concluded.
9. From the finished product results it was concluded that the process validation of Griseofulvin 375mg Tablets was concluded.

8. SCOPE FOR FUTURE STUDIES

1. Ongoing stability study (Accelerated and Long term) is to be carried out for the Griseofulvin 375mg Tablets.
2. Any changes in the manufacturing formula, manufacturing process etc of Griseofulvin tablets may leads to revalidation of the same.

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